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ANTRECTOMY WITH VAGECTOMY FOR CHRONIC DUODENAL ULCER

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THE search for the best surgical procedure for the treatment of duodenal ulcer continues in many centers throughout the world. For many years we employed either a partial gastrectomy alone or combined with a bilateral vagus resection as the operation of choice for this condition. Even though our results were more than satisfactory, in either group,[1-4] we continued to develop and evaluate other newer surgical procedures.

On July 1, 1957, we began to utilize an antrectomy and bilateral infradiaphragmatic vagus resection in all patients coming to surgery for the treatment of chronic duodenal ulcer.

PURPOSE

The purpose of this report is to present our results of this procedure of antrectomy and vagus resection. The selection of patients for surgical intervention was based upon the universally accepted criteria. These are hemorrhage, perforation, obstruction, recurrent ulceration, pain, and intractability. This report includes 115 consecutive male patients treated for chronic duodenal ulcer on the surgical service of this hospital from July 1, 1957, to Jan. 1, 1959.

AGE INCIDENCE

The average age was 49.3 years; the youngest was 24 years and the oldest was 71 years of age. The greatest number, 34.7 per cent, were in the 40 to 49-year-old age group. However, 28.8 per cent were over 60 years old (Table I). These two larger age groups correspond to the current average ages of the veterans of World Wars I and II.

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TABLE I. AGE DISTRIBUTION

AGE	NUMBER	PER CENT
20-29	2	1.7
30-39	25	21.9
40-49	40	34.7
50-59	15	13.0
60-69	31	27.0
70-79	2	1.7
Total	115	100

DURATION OF SYMPTOMS AND PREOPERATIVE COMPLICATIONS

The average duration of symptoms prior to resection was 11.5 years. In a high percentage of cases, the patients experienced various complications. The greatest number had pain and intractability and/or gastrointestinal bleeding. Of the group with bleeding (45 per cent), 26 per cent were classified as massive, 9 per cent moderate, and 10 per cent minimal. In 5 per cent perforation had occurred. Ten per cent developed pyloric obstruction.

As a result of these complications, other surgical procedures had been performed prior to institution of final definitive surgery (Table II).

TABLE II. PREVIOUS SURGICAL PROCEDURES

TYPE	NUMBER	PER CENT
Gastroenterostomy	4	3.5
Partial gastrectomy	2	1.7
Perforated ulcer, closure	3	2.6
Total	9	7.8

PREOPERATIVE GASTROINTESTINAL BLEEDING

In this survey are included all the cases in which bleeding occurred. As noted previously 45 per cent gave a history of bleeding or were admitted during an episode of hemorrhage. Antrectomy and vagectomy was performed in 22 per cent of the patients as an emergency procedure. In every case except one the ulcer was removed.

TABLE III. AGE INCIDENCE AND DEGREE OF BLEEDING

AGE	NUMBER OF PATIENTS	TYPE OF BLEEDING—PER CENT OF TOTAL 115		
		MASSIVE	MODERATE	MINIMAL
20-29	3	3	0	0
30-39	14	6	4	2
40-49	15	5	3	5
50-59	5	3	0	1
60 or over	15	8	2	3
Total	52 (45%)	25%	9%	11%

Twenty-seven patients (52 per cent) had recurrent episodes of bleeding preoperatively. In all but 2 cases the bleeding had occurred more than once (Table IV).

TABLE IV. AGE INCIDENCE AND RECURRENT HEMORRHAGE

AGE	NUMBER OF TIMES HEMORRHAGE OCCURRED				
	1	2	3	OVER 3	TOTAL
20-29	0	0	1	2	3
30-39	0	0	2	7	9
40-49	2	6	1	1	10
50-59	0	0	1	1	2
60 or over	0	0	3	0	3
Total	2	6	8	11	27 (52%)

PREOPERATIVE GASTRIC ANALYSIS

Preoperative gastric analysis for free acids in the fasting stomach, after Histolog injection and after Hollander's insulin test, was performed in all cases except in those patients with active hemorrhage. In 62 (53 per cent) of the patients free hydrochloric acid was present in the fasting stomach in amounts higher than 35 units; after Histolog injection in 80 (69 per cent) and in 112 (98 per cent) patients free acids over 35 units were revealed.

The 12-hour night volume resting secretion studies revealed the average volume of 920 c.c. in each patient with a maximum of 3,400 c.c. in one patient.

TYPE OF OPERATION PERFORMED

The procedure was accomplished through a supraumbilical, elliptical, transverse, or right subcostal transrectus abdominal incision. The vagectomy was performed after mobilization of the lower esophagus through the esophageal hiatus. The vagus nerves and their branches were completely dissected free for a distance of about 3 to 4 inches from the esophagus to the stomach. This portion of the vagal pathways was resected.

The antral portion of the stomach was resected. About 25 per cent of the stomach was removed from just distal to the pyloric ring to a point where the rugae began in the lower one-third of the stomach. This segment we considered grossly as the antrum; representing one-fourth or less of the stomach.

The duodenal ulcer was resected in 69 (60 per cent) of this series of cases. This included all the patients hemorrhaging from the ulcer except one. In the remaining 40 per cent the ulcer was not disturbed.

An antecolic gastrojejunal anastomosis (except in one), Polya type, was accomplished using a short afferent jejunal loop. In 14 per cent of the cases in this series a Hofmeister type of anastomosis was performed.

The abdominal wounds were closed by approximating the anterior and posterior rectus sheaths with interrupted fine silk sutures. The majority of the patients were ambulatory on the first day.

RESULTS

The follow-up studies were conducted at 6-month intervals. The first 6 months the patients were seen as outpatients, however, at 12 months and yearly intervals thereafter the patients were admitted to the hospital for a complete clinical and laboratory evaluation.

During the first 6 months of the follow-up study period 108 patients were seen; 75 patients had a 12-month follow-up and 15 completed an 18-month check-up.

POSTOPERATIVE COMPLICATIONS

Twenty-seven patients (23.4 per cent) developed postoperative complications. The type and number are listed in Table V. The most frequent complications were gastric atony (delayed emptying), hepatitis or homologous serum jaundice, and pulmonary.

TABLE V. POSTOPERATIVE COMPLICATIONS (IN 27 PATIENTS)

TYPE	NUMBER	PER CENT
Wound		
Abscess	1	0.86
Dehiscence	1	0.86
Pulmonary		
Atelectasis	3	2.58
Infarction	1	0.86
Miscellaneous		
Abscess, subhepatic	2	1.72
Atony, gastric	9	7.74
Diarrhea, mild, nonspecific	2	1.72
Diarrhea, enterocolitis, specific	1	0.86
Hepatitis	3	2.58
Hypoprothrombinemia	1	0.86
Jaundice, homologous serum	2	1.72
Jaundice, transient	1	0.86
Leak, duodenal stump	1	0.86
Oliguric uremia	1	0.86
Pancreatitis, acute	1	0.86
Peritonitis, acute	1	0.86
Psychosis	1	0.86
Total	32	27.5

POSTOPERATIVE DEATHS

There was *one (0.87 per cent) postoperative death,* which was due to an acute necrotizing pancreatitis. This patient did poorly immediately following operation. He had a large penetrating chronic ulcer involving the head of the pancreas; the superior rim of the ulcer was close to the pyloric ring. In order to obtain a safe closure of the duodenal stump, it appeared necessary to resect the ulcer.

It is important to note that no deaths occurred in the 52 (45 per cent) patients with bleeding and particularly noteworthy is the fact that no deaths occurred in 23 (22 per cent) patients who were operated upon as an emergency procedure during the time of continued and/or massive bleeding.

POSTOPERATIVE GASTRIC ANALYSIS

In all patients studied (108), repeated gastric analyses of the fasting specimen, after Histolog injection and after Hollander's insulin tests, revealed no free hydrochloric acid. This achlorhydric state has persisted in all cases.

The 12-hour volume of the resting gastric night secretions was reduced from a preoperative average of 920 c.c. to an average of 320 c.c.

POSTOPERATIVE GASTROINTESTINAL ROENTGENOGRAPHIC STUDIES

Repeated postoperative follow-up gastrointestinal roentgenographic examinations revealed a satisfactorily functioning stoma in 75 patients examined. The average emptying time of the gastric remnant within 6 months after surgery was 80 minutes. However, by the end of the first year in this same group the emptying was considered normal, with complete emptying in 30 to 40 minutes.

Repeated motor meal roentgenographic studies of the small bowel in 52 cases revealed that dumping, segmentation, puddling, and hypomotility with a delayed transit time existed in 40 per cent. However, even though these changes were seen on x-rays, the patients had no signs or symptoms related to a disturbed motor function. By the end of the first year, a repeat examination in 90 per cent of the 52 patients revealed the motor meal studies to be within normal range without any further evidence of disturbed motility or pattern.

EVALUATION OF FOLLOW-UP STUDIES

All patients gained weight following surgery. By the end of the first 6 months postoperatively, the patients reached their preoperative weight. By the end of the first year, the average weight gain was 10 pounds and by the end of 18 months the average gain in weight was 14 pounds. In addition to this favorable response, 95 per cent of the patients maintained themselves on three meals a day with an occasional snack between meals, without any major restrictions in dietary measures.

Diarrhea and the dumping syndrome were infrequent and were not seriously handicapping any patient. In fact, after a period of readjustment there were no cases of persistent or recurrent episodes of diarrhea. The dumping syndrome occurred in 4 per cent of this group (Table VI).

TABLE VI. RESULTS OF FOLLOW-UP STUDIES
(12 TO 18 MONTHS)

TYPE	NUMBER OF CASES
Weight	
Gain	75 (100%) 14 pounds average
Loss	0
Dumping syndrome	
Mild	3 (4%)
Diet	
Regular	75 (100%)
Restricted	0
Diarrhea	0
Meals	
Three times a day	75 (100%)
Pain	
No pain	73 (97%)
Distress with overindulgence	2 (3%)
Ability to work	
Good	60 (80%)
Poor	7 (9%)
Unable	8 (11%)

In the group of patients unable to work or who did poorly at work, a large per cent were patients who were retired, were disabled because of other diseases or conditions, pensioned, or were inmates of a mental hospital. Some patients tired easily at their type of work; they are included in the 9 per cent. However, it must be pointed out that a greater number in this category were elderly patients.

At the present time there is no evidence of marginal or recurrent ulceration in this entire series.

The over-all evaluation of the results in 115 patients was considered excellent to good in 94 per cent of the cases.

COMMENT

This procedure to date has proved more effective in acquiring the desired results in the treatment of chronic duodenal ulcer than any other operation we have employed in the past. It can be accomplished with a lower morbidity and mortality than most other surgical procedures currently being used.

It is interesting to note that in 85 per cent of these cases the procedure was performed by the senior house officers under the direct supervision of the full-time surgical staff. The operating time required is at least one-half of that of a partial gastrectomy with or without a vagus resection. Too, it is important to point out that there was only one death (0.087 per cent) in this series and that no deaths occurred in the 23 cases operated upon as an emergency during continued or massive bleeding.

The hospital stay was shortened by 2.5 days as compared to other surgical procedures formerly used by us for this condition.

If achlorhydria persists as it has to date in 75 patients for 12 to 18 months, it is unlikely that a recurrent or marginal ulcer will develop in this group of patients.

The minimal complaints, no bowel disturbances, continued gain in weight on three unrestricted meals per day, rapid rehabilitation, freedom from signs and symptoms of the ulcer syndrome all point to this procedure as being the operation of choice. In fact, we are now using it to the exclusion of all the others.

The ulcer is usually left in situ. The only time the ulcer is removed is in patients with active bleeding at the time of surgery or when the ulcer is so situated as to prevent a safe closure of the duodenal stump. In the majority of instances the ulcer can be left in situ and by so applying such a policy many of the hazards, risks, and difficult problems are eliminated. This certainly contributes to a lower morbidity and mortality.

Nasogastric suction is discontinued as soon as bowel sounds are heard; this usually occurs about the second or third postoperative day. Prolonged suction is no longer used even in the presence of delayed gastric emptying. Even though, in some patients, the retention of food or liquid gastric content is 1,000 c.c. or more, suction is discontinued. If the patient has distress as a result of overdistention from delayed gastric emptying, intermittent gastric aspiration is performed.

SUMMARY AND CONCLUSIONS

Antrectomy with bilateral infradiaphragmatic vagus resection for chronic duodenal ulcer is at the present our operation of choice. Its advantages include: (1) lower morbidity and mortality, (2) more rapid rehabilitation, (3) less side

effects, (4) shorter operating time and hospital stay, (5) least chance, if any, for recurrent or marginal ulcer formation, and (6) over-all results superior to practically all other operative procedures.

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A COMPARATIVE STUDY OF THE HYDROGEN ION CONCENTRATION IN THE RESIDUAL GASTRIC POUCH FOLLOWING VAGOTOMY, ANTRECTOMY, AND GASTRODUODENOSTOMY AND FOLLOWING VAGOTOMY, ANTRECTOMY, AND GASTROJEJUNOSTOMY

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IN REGARD to the operative therapy for duodenal ulcer, an appreciable number of reports have appeared in the recent surgical literature emphasizing the relatively high rate of recurrent ulceration following subtotal gastric resection when gastrointestinal continuity is re-established by end-to-end gastroduodenostomy (Billroth I method).[3, 7, 9, 14, 15, 17, 19, 20] There can be no doubt that a certain percentage of these recurrences can be attributed to the fact that an insufficient amount of gastric tissue was removed at the time of resection. Another factor sometimes mentioned as a possible contributing agent in producing recurrent ulceration when the Billroth I method is employed is the lack of adequate duodenogastric regurgitation of biliary, pancreatic, and small intestinal contents, thus producing little buffering effect on the residual gastric acidity. On the other hand, when the Billroth II method of reconstruction is utilized, Walters and others[19, 20] feel strongly that jejunogastric regurgitation is of prime importance in producing a buffering-like effect at the stomal site and this, in turn, is responsible for the low rate of recurrent ulceration associated with the latter method. Walters is of the opinion that the degree of duodenogastric regurgitation following a Billroth I reconstruction is less pronounced as compared to jejunogastric regurgitation, and no doubt the increased incidence of recurrent ulceration with the Billroth I method is due to the inadequate buffering effect of the small bowel contents on the residual gastric acidity.

Ideas regarding the importance of enterogastric regurgitation and its effect on the reduction of gastric acidity have varied widely. In the particular experimental preparation devised by McCann,[13] in which the total duodenal contents were shunted into the fundus of stomach, jejunal ulceration was produced in 80 per cent of the animals. Maier,[12] using a somewhat similar preparation, could produce only rarely a jejunal ulcer and he felt that the low incidence of ulceration might possibly be attributed to the larger gastroenterostomy stoma which he employed, as contrasted with the small stoma used in McCann's experiments. Maier, however, did note considerable diminution in

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gastric acidity following the shunt procedure. Graves[4] and Ivy[8] diverted the duodenal contents into the antrum of the stomach and failed to produce jejunal ulceration as McCann had done using the duodenofundic shunt. Wilhelmj[23] was able to prevent ulceration by anastomosing the duodenum to the gastric wall. He felt that the efficacy of duodenal secretions in lowering gastric acidity was due more to dilution than to neutralization. Owings and Smith[16] produced Mann-Williamson ulcerations and noted that some of the ulcerations healed when the duodenal contents were shunted back into the stomach. Lannin[11] carried out antral resection and later total duodenal regurgitation with the development of typical jejunal ulcers. Wilhelmj[22] subjected 2 animals to gastroduodenostomy and 2 others to gastroenterostomy. In all 4 animals he observed that large amounts of duodenal contents entered the stomach. He concluded that the presence of a large amount of duodenal secretions in the stomach could produce a hypersecretion of gastric juice, which was evident only after the stomach had been stimulated to secrete by histamine and not in the unstimulated stomach.

Kesavalu[10] drained the duodenal contents into the fundus of the stomach and employed a reverse intestinal fistula in the pyloric region in his animals for the purpose of detailed study. He concluded from his experiments that the presence of even the entire duodenal contents in the stomach did not cause effective neutralization, buffering, or dilution of gastric acidity in the fasting or digestive state. He felt that it was questionable if the slight and infrequent duodenal regurgitation that occurred normally could be a primary and essential factor in controlling gastric acidity. Boldyreff,[1] on the other hand, expressed the view that duodenal regurgitation was essential for the lowering of gastric acidity.

Little work has been done to prove or disapprove the effectiveness of duodenal secretions in altering the acidity of the gastric juice in man. Schmilinsky[18] established total regurgitation in 3 patients with marginal ulceration which had occurred after simple gastroenterostomy. One patient died postoperatively, one developed perforation of a new marginal ulcer, and the third patient suffered from a severe gastritis. Wangensteen[21] established total enterogastric regurgitation in 3 patients following antral excision and 2 of the 3 patients developed jejunal ulcers.

During the past 12 years, patients with duodenal ulcer requiring surgical treatment on our service have been subjected to bilateral subdiaphragmatic vagotomy combined with removal of the gastric antrum. The Billroth II method of gastrointestinal reconstruction was utilized almost exclusively during the earlier years, but within more recent years an increasing number of patients have been subjected to an end-to-end gastroduodenostomy following bilateral vagotomy with antrectomy (Figs. 1 and 2). Our observations now over a period of several years suggest that the incidence of recurrent ulceration associated with the Billroth I method appears to compare quite favorably with the low recurrence rate following a Billroth II reconstruction.[5, 6]

The purpose of the present communication is to tabulate the relative degree of peptic activity in the residual gastric pouch of patients who have had complete vagotomy, antral resection, and a Billroth II reconstruction and to compare the peptic activity to a group of patients who underwent essentially the same operative procedure with the exception that gastrointestinal continuity was established utilizing the Billroth I method.

The relative degree of peptic activity in the residual gastric pouch can best be determined by measuring the hydrogen ion concentration in the gastric juice under basal conditions, following ingestion of a test meal, and after stimulation with histamine. Peptic activity is reduced to a minimum or negligible degree in a pH environment of 4.5 or greater. When the pH of the gastric juice, however, is between 3.5 and 4.5, the possibility of recurrent ulceration is indeed unlikely.

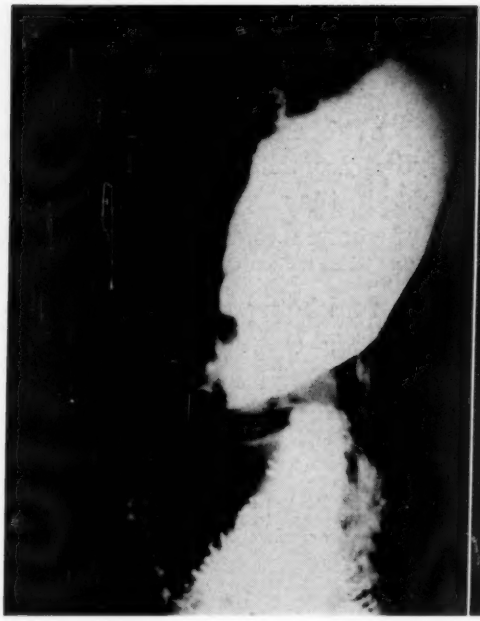

Fig. 1.

Fig. 2.

Fig. 1.—Barium study following bilateral vagotomy and antrectomy with end-to-end gastroduodenostomy.

Fig. 2.—Barium study following bilateral vagotomy and antrectomy with a Billroth II type of reconstruction.

In the normal individual the pH of the gastric juice under basal conditions is approximately 4.5, but upon stimulation with a test meal or histamine, the pH may fall to values of 2.5 to 1. In the individual with an active duodenal ulcer, the pH of the gastric juice under fasting conditions is in the approximate range of 2 to 2.5; whereas, upon stimulation with appropriate stimuli, the pH may fall to levels of 1.5 to 1.

METHOD

Following a 12-hour fasting period, a Levin tube is introduced and the stomach is emptied of its contents and the secretions discarded. After a 10- to

15-minute period of adjustment, the stomach pouch is aspirated at 10-minute intervals for a period of one hour. The volume of gastric juice obtained is recorded and pH determinations performed using a Beckman pH meter. Fifty cubic centimeters of 7 per cent alcohol is next introduced into the gastric pouch, and after a period of 30 minutes the gastric contents are removed at intervals of 10 minutes for a period of one hour. Volume determinations and pH values are again carried out. Histamine (0.5 mg.) is next given intramuscularly, and after 30 minutes gastric secretions are aspirated at 10-minute intervals for one hour. Similar determinations are performed. After an additional period of adjustment, or at a future date, a standard insulin test is performed to determine completeness of the vagal resection. From 20 to 40 units of regular insulin is administered intravenously, depending on the size and weight of the individual. Gastric secretions are then obtained at 30-minute intervals for a period of 2 hours and free acidity and pH values are determined.

pH DETERMINATIONS

Twenty-six unselected patients who had previously undergone bilateral vagotomy and antral extirpation, with continuity established by end-to-end- gastroduodenostomy, were subjected to study. The interval of time elapsing since the gastric surgery varied from 1 to 4 years. Among the 26 patients, 3 were found to have a positive gastric secretory response to insulin hypoglycemia. In the remaining 23 patients with a negative insulin test, the fasting pH of the gastric juice was found to vary from 4.3 to 7.8, with only 4 of the 23 patients having a basal pH value below pH 5. In most instances the pH was in the range of neutrality (pH 7). Upon stimulation with 7 per cent alcohol, the pH of the gastric juice in one instance dropped to 3.8, but no free hydrochloric acid response was obtained in the aspirated gastric specimen. The pH values ranged below pH 5 in 4 of the 23 patients upon stimulation with alcohol, and in the remaining 19 patients the pH values varied from 5 to 8. When histamine was used as a stimulant, the pH ranged from 2.1 to 4 in 6 of the 23 patients. The free HCl varied from 0 to 15 clinical units among the 6 patients. In the remaining 17 patients the pH of the gastric juice varied from 4.1 to 7.8 for an average of pH 5. No free HCl response was noted in the latter patients. The hourly secreting volumes following alcohol and histamine stimulation have been exceedingly low, ranging from 0 to 50 c.c. The hourly milliequivalents of free hydrochloric acid postoperatively have usually been 0, but in a few instances have been less than 1 mEq. (Table I).

Twenty-six unselected patients who underwent bilateral vagotomy and antrectomy with a Billroth II reconstruction likewise were subjected to pH studies of the gastric contents under basal conditions and following stimulation with a test meal and histamine. The group of patients had been followed from 1 to 10 years postoperatively at the time of the study. Insulin hypoglycemia failed to elicit the presence of free HCl in the gastric pouch of any of the 26 patients, thus indicating a complete interruption of the parasympathetic pathway in each instance.

TABLE I. POSTOPERATIVE pH DETERMINATIONS OF THE GASTRIC JUICE IN PATIENTS UNDERGOING BILATERAL VAGOTOMY AND ANTRECTOMY WITH BILLROTH I RECONSTRUCTION

CASE NUMBER	FASTING SPECIMEN	7 PER CENT ALCOHOL	HISTAMINE	INSULIN RESPONSE
1	6.9	6.6	2.2	Negative
			Free HCl-15 U	
2	6.9	6.7	4.1	Negative
			Free HCl-0 U	
3	6.6	7.0	4.4	Negative
			Free HCl-0 U	
4	7.3	7.1	6.4	Negative
5	6.3	6.3	4.5	Negative
			Free HCl-0 U	
6	6.9	6.9	6.0	Negative
7	5.0	5.5	5.3	Negative
8	2.9	2.4	1.4	Positive
	Free HCl-1 U	Free HCl-1 U	Free HCl-50 U	
9	6.6	6.7	2.9	Negative
			Free HCl-1 U	
10	7.0	4.4	3.7	Negative
		Free HCl-0 U	Free HCl-0 U	
11	7.2	2.3	2.0	Positive
		Free HCl-2 U	Free HCl-5 U	
12	7.4	8.0	7.0	Negative
13	5.5	6.3	6.3	Negative
14	6.0	6.2	6.0	Negative
15	4.6	4.5	4.5	Negative
		Free HCl-0 U	Free HCl-0 U	
16	7.4	7.0	6.1	Negative
17	7.8	7.1	7.5	Negative
18	7.5	6.8	5.4	Negative
19	7.1	6.5	2.1	Negative
			Free HCl-10 U	
20	4.4	4.6	4.0	Negative
	Free HCl-0 U	Free HCl-0 U	Free HCl-0 U	
21	4.3	3.8	4.2	Negative
	Free HCl-0 U	Free HCl-0 U	Free HCl-0 U	
22	6.2	6.5	6.7	Negative
23	7.1	7.3	7.2	Negative
24	4.6	3.6	1.7	Positive
		Free HCl-0 U	Free HCl-20 U	
25	6.8	6.7	5.0	Negative
26	4.9	5.7	2.7	Negative
			Free HCl-2 U	

Under basal conditions of study, the pH of the gastric juice among the 26 patients varied from 4.1 to 7.9, with a mean pH of 6.5. Upon stimulation with alcohol, the pH dropped below pH 4 in only one instance and this patient had no demonstrable free hydrochloric acid response to Töpfer's reagent. The average pH in the group with alcohol stimulation was 6.2. Following the introduction of histamine the pH dropped to values between 2.6 and 4 in 4 of the 26 patients. The resulting free hydrochloric acid response at this pH level, however, did not exceed 8 clinical units in any of the 4 patients. Many of the remaining 22 patients were found to have a pH approaching neutrality, with the mean pH of the entire group averaging pH 5.4. Following vagotomy, antrectomy, and Billroth II reconstruction, the hourly secretory volumes have likewise varied from 0 to 50 c.c. and the resultant hourly milliequivalents of free hydrochloric acid have usually been 0, or less than 1 mEq. in a few instances (Table II).

TABLE II. POSTOPERATIVE pH DETERMINATIONS OF THE GASTRIC JUICE IN PATIENTS UNDERGOING BILATERAL VAGOTOMY AND ANTRECTOMY WITH BILLROTH II RECONSTRUCTION

CASE NUMBER	FASTING SPECIMEN	7 PER CENT ALCOHOL	HISTAMINE	INSULIN RESPONSE
1	5.7	4.4	4.5	Negative
2	7.7	6.5	5.7	Negative
3	4.2	4.1	4.1	Negative
	Free HCl-0 U	Free HCl-0 U	Free HCl-0 U	
4	6.1	6.1	2.6	Negative
			Free HCl-5 U	
5	7.4	7.0	4.4	Negative
6	6.8	7.2	6.2	Negative
7	6.0	6.1	5.8	Negative
8	7.0	6.7	5.5	Negative
9	5.5	6.2	3.7	Negative
			Free HCl-8 U	
10	7.5	7.7	7.7	Negative
11	6.5	6.6	4.5	Negative
12	7.0	6.6	6.4	Negative
13	7.9	7.0	6.1	Negative
14	4.1	3.9	3.5	Negative
		Free HCl-0 U	Free HCl-0 U	
15	6.8	6.4	6.8	Negative
16	6.6	6.8	6.6	Negative
17	7.0	6.6	5.7	Negative
18	6.6	5.8	5.2	Negative
19	6.6	4.2	4.2	Negative
		Free HCl-0 U	Free HCl-0 U	
20	6.0	6.8	4.1	Negative
			Free HCl-0 U	
21	7.5	7.6	7.2	Negative
22	6.7	6.9	6.7	Negative
23	5.7	6.3	6.0	Negative
24	6.9	6.7	7.0	Negative
25	6.9	6.8	6.5	Negative
26	5.7	5.2	4.0	Negative
			Free HCl-0 U	

DISCUSSION

Farmer[2] in a clinical experiment demonstrated the value of the neutralizing effect of regurgitant pancreatic, bile, and duodenal contents on the acidity in the stomach pouch of an early postgastrectomy patient. By applying suction to a catheter inserted into the duodenum just distal to the closed duodenal stump in a patient who had recently undergone bilateral vagotomy with a 50 per cent resection and a Hofmeister reconstruction, he was able to remove a portion of the pancreatic, biliary, and duodenal secretions. Under these conditions the pH of the gastric juice in the particular patient fell to within the pH range of an individual with an active duodenal ulcer. When suction on the catheter was discontinued, the entire duodenal contents again came in contact with the gastroenterostomy stoma and gastric pouch and the pH of the gastric juice promptly rose to a value approaching neutrality. This clinical experiment was applied to 2 other patients who presented difficult duodenal stump problems, but the comparative results of the pH determinations were less striking. An additional patient showed no appreciable change in the pH of the gastric juice when suction was applied to the duodenostomy catheter, but it was felt that inadequate aspiration of duodenal contents was responsible for the failure to obtain a change in hydrogen ion concentration.

In the first patient cited, diversion of a portion of the duodenal contents through the catheter appeared to have a striking effect on the hydrogen ion concentration in the gastric pouch and this strongly suggests the influence of the neutralizing effect produced by the intestinal juices. Farmer's data, however, would have been more convincing had he been able to present a larger series of patients, or at least if somewhat more comparable results had been observed among the 4 patients whom he studied.

Among the two groups of patients comprising the present study, the hydrogen ion concentration in the gastric juice has been quite similar. Patients who have undergone complete vagotomy and antrectomy with a Billroth I reconstruction have demonstrated, for the most part, an achlorhydria to various secretory stimuli and appear to be as well protected against recurrent ulceration from the physiologic viewpoint as do the group of patients who underwent a similar operative procedure but with a Billroth II type reconstruction (Table III).

TABLE III. A COMPARISON OF THE PH VALUES OF THE GASTRIC JUICE AMONG THE BILLROTH I AND BILLROTH II GROUPS OF PATIENTS

	BILLROTH I		BILLROTH II	
	AVERAGE	RANGE	AVERAGE	RANGE
Fasting HCl	pH 6.4	4.3-7.8	pH 6.5	4.1-7.9
Alcohol	6.3	3.8-8.0	6.2	3.9-7.7
Histamine	5.0	2.1-7.5	5.4	2.6-7.7

When gastric aspirations were performed in this study, a somewhat larger quantity of bile was usually recovered from the gastric pouch in those patients who had undergone a Billroth II type reconstruction, but the presence of bile was noted in the gastric contents of patients who had been subjected to end-to-end gastroduodenostomy. Farmer has postulated that it is quite possible after vagotomy and antrectomy that there occurs a great reduction in the volume and degree of free acidity of the gastric juice, but there may still persist a small residue of gastric juice of low pH value. In turn, this small residue of gastric juice may readily be neutralized by very small quantities of regurgitant duodenal contents.

SUMMARY

The hydrogen ion concentration in the residual gastric pouch was determined among a group of patients who had undergone bilateral vagotomy and antrectomy with end-to-end gastroduodenostomy (Billroth I) for treatment of duodenal ulcer. Similar studies were carried out among a group of patients who had been subjected to bilateral vagotomy, antrectomy, and gastrojejunostomy (Billroth II).

Comparable pH values of the gastric juice were noted in both groups of patients when they were challenged with the usual gastric secretory stimulants.

Patients who have undergone vagotomy and antrectomy with a Billroth I reconstruction appear to be as well protected against recurrent ulceration from the physiologic point of view as do the group who have undergone vagotomy, antrectomy, and a Billroth II reconstruction.

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CHOLEDOCHODUODENOSTOMY IN THE TREATMENT OF STENOSIS OF THE LOWER PORTION OF THE COMMON BILE DUCT

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STENOSIS of the terminal end of the common bile duct is a frequent finding in chronic disease of the biliary tract. The pathogenesis of this condition is not clear and many explanations have been offered. In chronic cholecystitis and cholelithiasis, stenosis of the common duct may be secondary to the chronic inflammatory process involving the biliary tract. In those cases in which there are stones in the common duct and in which there is a history of previous common duct exploration, trauma may also be a contributing factor. Various theories have been advanced to explain the development of stenosis of the terminal portion of the common duct in the absence of biliary calculi or of previous exploration of the duct. Trommald and Seabrook[15] thought that hypertrophy and stenosis of the sphincter were part of the general thickening of the common duct which followed chronic cholangitis. Doubilet and Colp[3] showed in experimental animals that instillation of 0.9 per cent hydrochloric acid into the duodenum in the region of the papilla of Vater produced spasm of the sphincter of Oddi and elevation of introductal pressure. They speculated that persistent spasm of the sphincter might lead to fibrosis. Giordano and Mann[5] observed, at postmortem examination of patients with chronic cholecystitis and duodenal ulcer, a distinct hypertrophy of the muscle bundles about the terminal portion of the common duct and as much as a 2 mm. thickening of the sphincter.

Imamoglu, Perry, and Wangensteen[7] produced fibrosis of the lower end of the common bile duct experimentally in various species of animals by suturing a small strip of cellophane, lightly dusted with dicetyl sodium phosphate, around the lower part of the duct. At postmortem examination there was a considerable degree of fibrosis with narrowing of the duct at the site of the cellophane application with dilatation of its proximal portion. In those animals in which the stricture was incomplete, stones were found frequently in the gall bladder, and to a lesser degree in the common bile duct. In the experimental animals so treated, biliary stones were found in 7 of 8 rabbits (87 per cent) within 4 to 16 weeks, in 2 of 8 dogs (25 per cent) in 4 to 20 weeks, and in 1 of 2 monkeys (50 per cent) in 19 to 22 weeks. These observers expressed the opinion that the bile stasis which resulted from the narrowing of the terminal portion of the common duct favored the formation of stones in these animals. They also postulated that partial obstruction of the terminal portion of the duct might play a significant role in the development of biliary stones in man.

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They stated that their clinical experiences supported that theory. Pikula and Dunphy[11] studied the relationship between incomplete stricture of the common bile duct and gallstone formation in 13 dogs. They followed a technique similar to that used by Imamoglu, Perry, and Wangensteen.[7] In 5 of the 9 dogs which developed incomplete stricture without acholic stools, friable pigment stones were found predominantly in the gall bladder and also in the common duct. The pathologic findings in the liver resembled closely those found in cholangiolitic cirrhosis in man, rather than those seen in uncomplicated cholelithiasis. Their study did not confirm the theory that biliary stenosis was a common cause of gallstone formation. They stated, however, that they could not exclude the possibility that a mild degree of stenosis or spasm of the lower part of the common duct might produce gallstones without associated liver damage. They also pointed out that such a relationship had been demonstrated clinically by various observers.

The surgical objective in the treatment of stenosis of the terminal portion of the common duct is to re-establish the free flow of bile into the gastrointestinal tract. The purpose of this paper is to describe our experience with the use of choledochoduodenostomy in 5 cases.

CASE REPORTS

CASE 1.—E. A. was a 71-year-old man who had had a subtotal gastrectomy for duodenal ulcer in May, 1953. At that time a choledochostomy had been performed and a T-tube had been inserted into the common duct to delineate it during the dissection of the duodenal ulcer from the pancreas. The patient made an uneventful recovery and was free of symptoms until September, 1957, when he began to experience epigastric pain. On Dec. 21, 1957, the night before admission, the pain became severe and persistent. On admission the patient was in severe distress. His temperature was 100° F. and the pulse rate was 80 per minute. The sclerae were slightly icteric. There was minimal tenderness in the right upper quadrant of the abdomen.

Laboratory findings: The white blood cell count was 11,950 with 80 per cent polymorphonuclear leukocytes; the total serum bilirubin was 5.1 mg. per cent; the alkaline phosphatase was 24.4 King-Armstrong units; the urine urobilinogen was 2.8 Ehrlich units. Roentgenograms of the abdomen showed a radiopaque shadow in the right upper quadrant which was suggestive of a gallstone. A cholecystogram, performed following administration of a double dose of dye, failed to delineate the gall bladder. An intravenous cholangiogram showed a dilated common bile duct with stenosis of its distal end.

An abdominal exploration was performed on Jan. 8, 1958. The gall bladder was distended and contained stones. The common bile duct was thick walled and dilated, measuring about 2 cm. in diameter. The common duct was opened and a large amount of sediment and many soft stones were evacuated. A ureteral catheter was passed with difficulty into the duodenum. A cholecystectomy and a choledochoduodenostomy were performed. The patient's postoperative course was uneventful. An intravenous cholangiogram performed on the fifteenth postoperative day showed good flow into the duodenum. The total serum bilirubin dropped to 1.6 mg. per cent and the alkaline phosphatase to 7.4 King-Armstrong units. The patient was discharged on Jan. 26, 1958, on the eighteenth postoperative day. He was symptom free at his last follow-up examination 11 months later.

Comment: In this case, stricture of the lower end of the common duct was the result of the close proximity of a duodenal ulcer or of trauma incurred during the operation for

duodenal ulcer. Dilatation and thickening of the common bile duct and the formation of stones in the duct ensued. The patient has been asymptomatic since choledochoduodenostomy was performed.

CASE 2.—F. B. was a 68-year-old white woman who had had a cholecystectomy for cholelithiasis in January, 1957. The patient was well until April, 1957, when she began to experience intermittent pains in the epigastrium. On May 1, 1957, the pains became severe and she was admitted to the hospital on the following day. On admission the patient was acutely ill. Her temperature was 102° F. and the pulse rate was 80 per minute. The sclerae were icteric; the abdomen was soft but tender.

Laboratory findings: The white blood cell count was 13,200 with 78 per cent polymorphonuclear leukocytes; the total serum bilirubin was 5.4 mg. per cent; the alkaline phosphatase was 39.9 King-Armstrong units. An intravenous cholangiogram, which had been performed on the day prior to admission, failed to reveal the ducts.

An operation was performed on May 9, 1958. The common duct was dilated and measured 2.3 cm. in diameter. The duct was explored and was found to contain much grumous material and many calculi. The wall of the duct was 3 mm. thick and its terminal end was markedly narrowed. A choledochoduodenostomy was performed. The patient's postoperative course was uneventful and she was discharged on the twentieth postoperative day. She was last seen in November, 1958, 6 months following the operation. At the time she was asymptomatic and her physical examination was negative.

Comment: This was a case of residual or recurrent stones in the common bile duct. The common duct was markedly dilated and thickened and its lower end was narrowed.

CASE 3.—A. R. was a 54-year-old woman who had had a cholecystectomy and common duct exploration in July, 1957. The duct had been dilated and thick walled and contained many calculi which had been removed. A T-tube was inserted. She was admitted to the hospital on Sept. 29, 1957, because of a persistent wound infection. A cholangiogram, performed through the T-tube showed residual stones in the common duct. Reoperation was performed on Oct. 7, 1957, and about 30 stones were removed from the duct. An operative cholangiogram was interpreted as negative for calculi. A T-tube was left in situ and she was discharged from the hospital on the tenth postoperative day. The tube was subsequently removed. The patient remained asymptomatic until Dec. 13, 1957, when she developed nausea, vomiting, and pain in the upper abdomen. She was admitted to the hospital for the third time. On admission the patient was acutely ill. Her temperature was 101.8° F. and the pulse rate was 120 per minute. The sclerae showed a slight degree of icterus. The abdomen was soft but there were tenderness and rebound tenderness in the epigastric area.

Laboratory findings: The white blood cell count was 7,500 with 68 per cent polymorphonuclear leukocytes; the total serum bilirubin was 4 mg. per cent; the alkaline phosphatase was 17.5 King-Armstrong units. An intravenous cholangiogram, performed on Dec. 23, 1957, revealed a slight degree of dilation of the common duct but no calculi. While in the hospital, the patient had recurrent attacks of severe epigastric pain and fever.

At operation on Jan. 20, 1958, the common bile duct was found to be dilated, measuring 2.5 cm. in diameter. Its wall was thickened to approximately 5 mm. Numerous stones were removed from the duct. A small French catheter could not be passed into the duodenum. It was felt that there was a stricture at the lower end of the duct and a choledochoduodenostomy was performed. At the completion of the anastomosis the stoma was 1½ inches in diameter. The patient's postoperative course was uneventful and she was discharged on the twelfth postoperative day. At the last follow-up examination in November, 1958, the patient was in excellent condition and had gained 40 pounds in weight.

Comment: This patient had had two previous common duct explorations for stones. At this operation the duct was found to be thickened and dilated and to contain many

stones. The lower end of the duct was narrowed. Since the performance of a choledochoduodenostomy the patient has been asymptomatic.

CASE 4.—Y. G. was a 57-year-old woman who had had a cholecystectomy in 1950 and a common duct exploration for stones in 1952. She had been asymptomatic until September, 1955, when she began to have recurrent attacks of epigastric pain. She was admitted on Dec. 13, 1955, following an attack of severe epigastric pain, nausea, chills, and fever. On admission the patient was comfortable. The temperature was 99.8° F. and the pulse rate was 76 per minute. The physical examination was negative.

Laboratory findings: The white cell count was 6,000 with 51 per cent polymorphonuclear leukocytes; the icteric index was 9; the alkaline phosphatase was 5.1 King-Armstrong units.

At operation the common bile duct was dilated, measuring 1.7 cm. in diameter, and its wall was quite thick. A number of stones were removed from the duct and a No. 12 catheter was easily passed into the duodenum. A choledochoduodenostomy was performed. The patient's postoperative course was uneventful and she was discharged 15 days after the operation. The last follow-up examination was performed in November, 1958, 2 years and 11 months after the operation at which time the patient was in excellent health.

Comment: This was the patient's third operation on the biliary tract and the second common bile duct exploration. Although the ampulla of Vater was patent, it was deemed advisable to perform a choledochoduodenostomy to eliminate stasis and to afford any calculi, which might form in the biliary ducts, free egress into the duodenum.

CASE 5.—M. S., a 65-year-old woman, had had a cholecystectomy and common duct exploration in February, 1953, at another hospital. The patient had been sent home with a T-tube in the common duct. In June, 1953, she developed signs of obstruction of the common duct and about 750 c.c. of dark bile was removed by drainage during a 24-hour period. The bile occasionally contained particulate matter. When the T-tube was clamped off, the patient developed chills, fever, and slight icterus. She was admitted to the hospital on Oct. 25, 1953. On admission she appeared to be chronically ill. Her temperature was 99.8° F. and the pulse rate was 80 per minute.

Laboratory findings: The white blood cell count was 5,450 with 5 per cent polymorphonuclear leukocytes; the total serum bilirubin was 4.3; the alkaline phosphatase was 8.0 King-Armstrong units. A cholangiogram performed through the T-tube revealed a stone in the common duct. Stools were occasionally clay colored.

At operation, 3 days after admission, the common duct was found to be dilated and its wall thickened. The duct was explored but no stones were found. The lower end of the duct was narrowed and even the smallest Archibald dilator could not be inserted into the duodenum. An attempt to explore the common bile duct through a duodenotomy incision also demonstrated a complete stricture of the ampulla. A choledochoduodenostomy was performed. The postoperative course was uneventful and she was discharged on the fourteenth day after the operation. The last follow-up examination was done in November, 1958, at which time the patient was well and had no complaints.

Comment: This was a case of complete stricture of the lower end of the common duct and ampulla. The patient has been well during the 5-year period following the performance of choledochoduodenostomy.

DISCUSSION

Dilatation of the sphincter of Oddi is the surgical procedure most frequently employed to relieve biliary obstruction due to stenosis of the terminal portion of the common duct. Colcock[2] reported good results following exploration of the duct and dilatation of the sphincter in a series of 100 consecutive

cases with residual common duct stones not associated with fibrosis of the sphincter. He followed 94 of these patients for periods of 4 to 6 years and found that only 2 patients required reoperation.

Sphincterotomy is another procedure in common usage. Cattell, Colcock, and Pollack[1] have reported good results following transduodenal sphincterotomy and the insertion of a long-arm T-tube. Eighty-one of a group of 100 patients treated in this manner were asymptomatic for 6 to 18 months. However, they considered this follow-up period too short to be conclusive. Various techniques of sphincterotomy have been described by Cattell,[1] Doubilet,[4] and more recently by Jones.[9]

Thompson and his associates[14] have called attention to the fact that acute pancreatitis may follow exploration of the common bile duct and that the incidence of this complication was increased by the insertion of a long-arm T-tube. The mortality rate associated with this complication was 77 per cent. Newman and Northup[10] have pointed out that the efficacy of sphincterotomy depends upon the completeness of the operation. If only the papillary fibers were divided, the more powerful choledochal muscle would be left intact and still capable of sphincteric action. It was their opinion that this muscle should also be divided in order to achieve a complete sphincterotomy. Under these circumstances, sphincteroplasty ceases to be a simple procedure and becomes a rather extensive and hazardous operation. Jones, Smith, and Gregory[9] have demonstrated that in patients who have had the usual type of sphincterotomy, the injection of morphine produced constriction of the lower end of the common bile duct as a result of the contraction of the duodenal wall. They believed that this finding was the reason why sphincterotomy for recurrent pancreatitis was frequently ineffective. They recommended a new operation which they called "sphincteroplasty."

We believe that exploration of the common duct and dilatation of its sphincter by the use of metallic instruments may be followed by iatrogenic complications. A false passageway may be created during this manipulation, especially if any degree of force is used. There is also the danger of producing postoperative pancreatitis and stricture formation.[14] Finally, the improvement obtained by dilating the narrowed terminal duct and sphincter may be only temporary. We also consider it impractical to attempt to drain a large and dilated duct through a relatively small opening. The discrepancy between the size of the common bile duct and the ampulla of Vater was probably the main reason for the formation of grumous material and stones in Case 4. We have, therefore, abandoned the use of metal dilators and are employing ureteral catheters and also urologic filiforms and followers during common duct exploration since they are less traumatic. When an absolute or relative narrowing of the lower end of the common bile duct is found at operation, we feel that an extensive sphincteroplasty or bypass operation should be performed. This situation would be comparable to the slow flow that occurs when fluid, especially if it is viscid, drains through a narrow outlet from a wide reservoir.

Procedures to bypass an obstruction in the terminal portion of the common duct by anastomosing the duct to the intestinal tract have generally fallen into

disfavor because of the fear of ascending infection in the biliary tract and liver, secondary to the reflux of intestinal contents. Hosford[6] and Sanders[12, 13] have reported excellent results with side-to-side choledochoduodenostomy. They believed that it is the procedure of choice, since it is simple to perform and it is based on sound physiologic principles. Iszak and Steiger[8] performed choledochoduodenostomy in 66 patients. In 56 cases this operation was done because of narrowing of the ampulla of Vater due to cicatrization or spasm of the sphincter of Oddi and in 10 cases for postcholecystectomy syndrome. These authors preferred choledochodenostomy to sphincterotomy because they felt that it was a simpler procedure and that it was followed by fewer complications. Forty-nine of their patients were followed for a period of 9 months to 7 years. They reported that none of them developed clinical signs of cholangitis, despite the fact that retrograde flow of barium into the liver was demonstrated radiographically in many postoperative patients.

Our technique of choledochoduodenostomy is easy to perform. The duodenum is mobilized by the Kocher maneuver. A choledochotomy incision is then made in the lower part of the common duct and the duct is explored. If it is decided that a choledochoduodenostomy is indicated, the incision is enlarged to about 2.5 cm. or more. A side-to-side anastomosis is then performed between the duct and the duodenum, using the inner layer of interrupted 3-0 chromic catgut and an outer layer of interrupted 3-0 black silk sutures. When completed, the stoma should measure 2.5 cm. In 4 of the cases we are reporting the indication for this procedure was stenosis of the lower end of the common duct. In one case we decided to perform this operation although stenosis was not demonstrated. It was our opinion that since this was the patient's third operation and her second common duct exploration, choledochoduodenostomy would be the procedure most likely to ensure permanent relief. In our cases this operative procedure did not present any unusual technical problems and was followed by an uneventful postoperative course. We were especially impressed with the fact that our patients remained asymptomatic. We attribute the good results to the fact that in each case the stoma between the common duct and the duodenum was large enough (2.5 cm. or more) to ensure its patency. It is possible that sphincteroplasty, as described by Jones,[9] may have been equally effective, but this procedure is more difficult to perform and may be followed by a higher incidence of complications. The length of the follow-up in our cases has varied from 6 months to 5 years. These studies have shown that the patients have remained well and show no evidence of recurrent biliary disease. Our experience, together with that of Sanders, Hosford, and others, makes us feel that side-to-side choledochoduodenostomy is an efficacious and safe operation.

CONCLUSIONS

1. Side-to-side choledochoduodenostomy is a simple and effective procedure for relieving biliary tract obstruction due to stenosis of the lower end of the common bile duct.

2. This procedure has also been used to prevent formation of recurrent common duct stones secondary to a relative stenosis.

3. The formation of a stoma, about 2.5 cm. or more in length, is essential since it ensures its patency and allows free drainage of the contents of the biliary tract into the duodenum.

4. No complications or recurrence of biliary tract disease during follow-up periods of 6 months to 5 years have occurred in the 5 cases reported.

ADDENDUM

Since completion of this paper, 6 additional patients have had choledochoduodenostomies performed, 3 as a primary procedure and the other 3 following previous operations on the biliary tract. In 1 case a stricture of the mid-portion of the common bile duct was found 1 year after a cholecystectomy and choledochostomy had been performed. It was possible to free the duodenum and to anastomose it widely to the proximal hepatic duct without tension. All these patients have had uneventful postoperative convalescences and are asymptomatic at the present time.

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ADENOCARCINOMA OF THE LARGE BOWEL

1,340 Cases With 100 Per Cent Follow-up

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ALTHOUGH the past century has witnessed publication of countless series of patients with large bowel carcinomas, relatively few have concerned groups of substantial size which have been followed without exception. Series sufficiently large in number to allow classification of lesions by site and stage and sufficiently well studied to permit complete follow-up would appear unusual.

The hazards of making evaluations of therapy based on information available from heterogeneously grouped cases become more apparent when more detailed classification of cases is made. Selective follow-up of cases—sometimes indicated by omission of "cases lost to follow-up," inclusion only of "patients who could be traced," or exclusion of those residing in another state or another country—tends to introduce errors which may defy precise evaluation.

The study of a substantial group of cases seen at the University Hospitals was done; follow-up of each case was included. Additional information is presented to allow some definition of the composition of the groups involved.

MATERIALS AND METHODS

Study was made of the records of patients with primary adenocarcinoma in the large bowel seen at the University of Minnesota Hospitals, 1940 through 1955. All cases were included, whether admitted to the hospital or not and whether or not given definitive therapy. Patients who had previously undergone treatment elsewhere and were referred here for palliative therapy, those with carcinoma metastatic to the bowel, and those with malignancies other than adenocarcinoma were not included.

Classification of cases was made according to area of bowel involved. Usually little or no question existed; in every instance, however, evidence available from surgeon, pathologist, and radiologist was correlated in placing the site of the lesion. For purposes of classification, the rectum proper (rectal ampulla or "true rectum") was considered the distal 10 cm. of large bowel above the anus, the rectosigmoid included the 10 to 16 cm. area, and the sigmoid colon was considered to extend from 17 cm. to the descending colon.[1-3]

Dukes' method was utilized to classify pathologic spread of tumor in excised lesions.[4] Lesions without definite spread to connective tissue or lymph nodes were classified as Dukes A; those with connective tissue spread, Dukes B; and only those with lymph node involvement were classified as Dukes C.

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Attention was directed to postoperative follow-up of patients. No patient was "lost to follow-up"; information was obtained as to whether the patient was alive or dead, and, if dead, the date of death. For the expired patients, in almost every case, evidence was available regarding detected or diagnosed tumor recurrence. Many of the living patients were examined at the University Hospitals or had been recently seen; most of the others were personally contacted; in the remaining instances, relatives, physicians, and so forth supplied authoritative information.

A total of 1,340 patients with adenocarcinoma primary in the large bowel comprise the over-all 1940 through 1955 group. A portion of the over-all group, the 1940 through 1950 series (follow-up studies of at least 5 years' duration), however, received greater attention and provided the most information regarding results of present-day therapy of bowel cancer. The portion of the 1940 through 1950 group with primary rectal lesions (including rectal ampulla and rectosigmoid) was studied in detail regarding curative results of various operative procedures in current use, and is presented elsewhere.[5]

CASES: 1940-1955

The over-all group of cases, consisting of patients with adenocarcinoma of the large intestine seen from 1940 through 1955, includes 693 cases with primary lesions in the rectum, 605 primary in the colon, and 42 patients with lesions present in several different anatomic sites of the large bowel (Table I). Further classification was made indicating patients subjected to excision procedures, those who did not undergo excision of the lesion, and a third group consisting of patients seen under circumstances which allowed diagnosis but precluded consideration of treatment (diagnosis made here but went elsewhere for treatment, refused treatment and left hospital without being treated, and a few who were moribund on admission and expired soon thereafter). Study of the 1940 through 1955 group and classification of cases allowed some definition of the composition of this over-all series, description of several diagnostic factors, and notation of therapeutic aspects. Since many of the diagnostic criteria and symptoms are well known, only more pertinent aspects are indicated.

TABLE I. ADENOCARCINOMA OF THE LARGE BOWEL (1940-1955)

	COLON	RECTUM	MULTIPLE SITES	TOTAL LARGE BOWEL
Lesions excised	484	523	39	1,046
Lesions not excised	82	126	3	211
Other	39	44	0	83
Total	605	693	42	1,340

Few cases were considered inoperable because of the extent of disease or were explored without performance of either a curative or palliative procedure; a total of 1,046 patients underwent excision procedures. The operative rate was 98 per cent. Resection rate was 84 per cent (over-all), with 87 per cent for colon and 82.3 per cent in the rectal cases.

Table II indicates cases subjected to surgical excision procedures (except those with cancers present at several different sites). The classification "palliative" was employed to separate from the curative group cases known at the time of operation to have allowed residual tumor to remain. Of the 1,007 cases, excisions in 364 of 484 colon cancer cases (76 per cent) were performed for cure; 405 of 523 rectal cancer excisions were curative. A few with records precluding classification as curative or palliative are listed as "indeterminate."

TABLE II. OPERATIVE PROCEDURES PERFORMED FOR ADENOCARCINOMA OF THE LARGE BOWEL (1940-1955)

	COLON	RECTUM	COLON AND RECTUM
Operative rate	98%	98%	98%
Total cases	566	649	1,215
Operation performed	556	635	1,191
Inoperable	10	14	24
Resection rate	87%	82%	84%
Total operative cases	556	635	1,191
Exploration only	14	6	20
Nonexcision, palliative procedures	58	106	164
Colostomy	41	105	146
Ileostomy	3	0	3
Cecostomy or enterostomy	7	0	7
Bypass procedure	7	1	8
Excisions	484	523	1,007
Regular excisions	393	463	856
Curative	296	359	655
Palliative	93	85	178
Indeterminate	4	19	23
Enlarged excisions	80	47	127
Curative	62	38	100
Palliative	18	9	27
Other excisions	11	13	24
Curative	6	8	14
Palliative	5	5	10

The term "enlarged excision" was employed to classify more accurately certain cases. Quite regularly patients are seen with lesions advanced beyond the boundaries encompassed by ordinary established operative procedures; at times, when cure or definite palliation appeared within the realm of possibility, excision of usual tissues, plus additional tissue necessitated by the extent of disease, has been done. Classifying these cases as "enlarged" excisions separated them from usual or "regular" excisions, allowed better evaluation of any curative merit they might have had, and did not confuse operative mortality for regular excision procedures with that for enlarged procedures which included excision of liver, urinary bladder, abdominal wall, and so forth.[17]

Some indication of the extent of malignant disease present in patients who underwent surgical excision procedures is indicated in Table III. Of the 755 patients who had excisions for cure (regular and enlarged), 13.25 per cent had lesions which could not be excised by the usual or regularly employed excision procedures but which required enlargement of the operative scope by inclusion of substantial additional tissue.

TABLE III. CURATIVE EXCISIONS PERFORMED FOR ADENOCARCINOMA OF THE LARGE BOWEL (1940-1955)

	COLON		RECTUM		COLON AND RECTUM	
	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
Regular excisions	296	82.7	359	90.4	655	86.75
Dukes A	128	35.7	156	39.3	284	37.6
Dukes B	62	17.4	63	15.8	125	16.55
Dukes C	106	29.6	140	35.3	246	32.6
Enlarged excisions	62	17.3	38	9.6	100	13.25
Total	358	100.0	397	100.0	755	100.0

Operative mortality for the 856 cases subjected to regular excision procedures (Table IV) was 5 per cent. Colostomy as a palliative procedure without excision of tumor had a 20 per cent operative risk, and enlarged excisions a 27 per cent rate.

TABLE IV. OPERATIVE MORTALITY FOR ADENOCARCINOMA OF THE LARGE BOWEL 1,129 Operative Procedures (1940-1955)

	COLON		RECTUM		COLON AND RECTUM	
	NUMBER OF CASES	OPERATIVE MORTALITY	NUMBER OF CASES	OPERATIVE MORTALITY	NUMBER OF CASES	OPERATIVE MORTALITY
Regular excisions	393	5.4%	463	5.2%	856	5.3%
Enlarged excisions	80	27 %	47	26 %	127	27 %
Colostomies	41	29 %	105	17 %	146	20 %

The lesions included in the over-all series, 1940 through 1955, were located in various areas of the large bowel; 53.4 per cent were in the rectum (distal 16 cm. of large bowel), and 46.6 per cent were in various portions of the remainder of the large bowel (Table V). When divided into right colon (transverse, hepatic flexure, ascending colon, and cecum) and left colon (sigmoid, descending, and splenic flexure), 22.6 per cent were present in the former and 24 per cent in the latter.

The mean admission hemoglobin values, ascertained for the individual patients with large bowel cancer, are summarized on Table V for 1,162 cases; the few patients who had transfusions prior to admission or with no recorded values are not included. Although average values associated with lesions at various sites may superficially appear similar, it may be noted that the number of cases often makes these modest difference of importance. For example, while the mean hemoglobin for cases of cecal cancer was 11 Gm. compared with 13 for the rectum, hemoglobin values of 10 Gm. or below were present in association with 47 per cent of the cecal lesions and only 15 per cent of the rectal lesions. Statistically, this difference is highly significant. Anemia (hemoglobin 10 Gm. or less) was present in 44 per cent of patients with right colon lesions, compared with 31 per cent of the transverse colon cases, 17.9 per cent of the left colon cases, and 15 per cent of the patients with rectal lesions.

CASES: 1940 THROUGH 1950

The patients with large bowel adenocarcinoma, seen from 1940 through 1950, were studied in more detail, especially in regard to results of surgical

TABLE V. ADENOCARCINOMA OF THE LARGE BOWEL

SITES OF LESIONS— 1,298 CASES 1940-1955	PER CENT OF TOTAL	ADMISSION HEMOGLOBIN—1,162 CASES				AGE AND SEX—689 CASES RESECTED 1940-1950			
		NUMBER OF CASES	MEDIAN HGB.	PER CENT 10 GM. OR LESS	PER CENT MORE THAN 14 GM.	NUMBER OF CASES	PER CENT MALE	MEDIAN AGE	
								MALE	FEMALE
Cecum	12.9	152	11	47	3	100	39	65	65
Ascending colon	3.4	40	12	30	10	20	40	65	52
Hepatic flexure	1.4	16	10.5	50	6	9	56	54	59
Transverse colon	4.9	59	12	31	8.5	37	40	63	67
Splenic flexure	1.4	15	12	20	13	8	50	59	52.5
Descending colon	3.7	44	12	11	20	31	45	59.5	57
Sigmoid colon	18.9	232	13	19	14	125	54	66	58.5
Rectum	53.4	663	13	15	14	359	61	64	60

treatment. As shown in Table VI (see also Table I), the total of 966 cases consisted of 433 patients with primary cancer in the colon, 501 in the rectum, and 32 primary lesions in several different sites in the large bowel. (The latter group was tabulated separately in subsequent tables; the 59 cases which could be considered not available for consideration of therapy—those listed as "other"—are not utilized in most of the subsequent computations.)

TABLE VI. ADENOCARCINOMA OF THE LARGE BOWEL
(1940-1950)

	COLON	RECTUM	MULTIPLE SITES	TOTAL LARGE BOWEL
Lesions excised	330	359	29	718
Lesions not excised	74	112	3	189
Other	29	30	0	59
Total	433	501	32	966

A total of 853 of the 875 patients with large bowel cancer were subjected to operation (Table VII); more than 97 per cent of these patients were operated upon. Excisions were done on 78.3 per cent of the patients with rectal lesions operated upon and 83.5 per cent of those with colon lesions. Many of the patients who underwent operation but not excision had palliative procedures performed and are considered in more detail later.

Several additional aspects of the cases subjected to excision are also shown in Table VII (see also Table II). Of the 689 excisions performed, 532

TABLE VII. TREATMENT EMPLOYED FOR ADENOCARCINOMA OF THE LARGE BOWEL
(1940-1950)

	COLON	RECTUM	COLON AND RECTUM
Operative rate	97.7%	97.3%	97.5%
Total cases	404	471	875
Operations performed	395	458	853
Inoperable	9	13	22
Resection rate	83.5%	78.3%	80.7%
Total operative cases	395	458	853
Exploration only	11	5	16
Nonexcision, palliative procedures	54	94	148
Colostomy	38	93	131
Ileostomy	3	0	3
Cecostomy or enterostomy	6	0	6
Bypass procedure	7	1	8
Excisions	330	359	689
Regular excisions	256	318	574
Curative	199	250	449
Palliative	56	55	111
Indeterminate	1	13	14
Enlarged excisions	65	31	96
Curative	50	23	73
Palliative	15	8	23
Other excisions	9	10	19
Curative	5	5	10
Palliative	4	5	9

(77.1 per cent) were performed for cure. The great majority of the curative excisions were of the regular variety, that is, 449 of 532 (84.3 per cent).

The median ages of male and female patients and the percentage of male patients in each group are shown in Table V for those with lesions present in the several areas of the large bowel. It may be noted that while 54 per cent of the entire group was composed of male patients, 63 per cent of patients with cancers of the rectal ampulla were male, and 61 per cent of patients with cecal cancers were females. Statistical analysis indicated that the cecal-rectal, male-female difference is very significant. Also, although more cecal lesions were present in females and most rectal lesions were in males, more females had rectal lesions than had cecal lesions.

The results of excisions for carcinoma of the large bowel, revealed by 5-year follow-up, are shown in Table VIII for the 522 patients who underwent excisions for cure, 1940 through 1950. Results of treatment of patients with rectal cancer are presented in more detail elsewhere, but survival figures, as well as totals for large bowel cancers, are herein tabulated. Patients with cancers of the right colon showed the most favorable prognosis: 88 per cent 5-year survival with Dukes A lesions, 69.5 per cent for the average of A, B and C lesions, and 39.1 per cent for the more extensive lesions which required enlarged excisions. Note that the results for patients with rectal cancer were less favorable than those for either the right or left colon or for the average of the entire colon, as well as for the average of the entire large bowel. (Hospital deaths have been deducted in computation of these figures.)

Table IX presents a summary of the 5-year survival data for curative excisions for the various anatomic sites in the colon. The 5-year survival rate of 90 per cent associated with lesions of the transverse colon and the 80 per cent rate noted for the small hepatic flexure group are of interest.

What might be termed an "over-all clinical cure rate" for patients with lesions at the various sites in the bowel is shown in Table X. The totals include patients who were considered inoperable, had a laparotomy only, or had palliative procedures (including palliative excisions), and all who underwent curative excisions. Only the patients who refused treatment, went elsewhere for therapy, or arrived moribund are excluded. Patients considered "cured" in this computation survived 5 or more years postoperatively without evidence of recurrent cancer. Hospital deaths are not deducted. It may be noted that this particular tabulation serves to emphasize over-all prognosis for patients with lesions at each of the several sites, rather than providing direct evaluation of operative procedures employed. Again the transverse colon was associated with a favorable prognosis; a 46 per cent rate was present.

During the period 1940 through 1950, 111 palliative excisions of the regular variety were performed. Table XI tabulates palliative excisions, other palliative procedures, and certain other cases; subsequent survival is noted. The 111 palliative excisions (56 colon and 55 rectum) are of the 1940 through 1950 series. The remaining cases are of the 1940 through 1955 group. It may be noted that in the cases of carcinoma of the colon, while palliative excision was

TABLE VIII. 5-YEAR SURVIVAL RATES FOR CURATIVE EXCISIONS OF ADENOCARCINOMA OF THE LARGE BOWEL*
(1940-1950)

	RECTUM		LEFT COLON		RIGHT COLON (INCLUDING TRANSVERSE)		TOTAL COLON		TOTAL LARGE BOWEL	
	NUMBER OF CASES	PER CENT 5-YR. SURVIVAL	NUMBER OF CASES	PER CENT 5-YR. SURVIVAL	NUMBER OF CASES	PER CENT 5-YR. SURVIVAL	NUMBER OF CASES	PER CENT 5-YR. SURVIVAL	NUMBER OF CASES	PER CENT 5-YR. SURVIVAL
Regular excisions										
Dukes A	108	70	43	77	44	88	87	83	195	75.5
Dukes B	43	51	20	83	18	53	38	68.5	81	59
Dukes C	99	24	39	37	35	54.5	74	45	173	33
Total regular excisions	250	49	102	63	97	69.5	199	66	449	56
Enlarged excisions	23	17	22	33	28	39	50	37	73	30

*Hospital deaths excluded in computations.

TABLE IX. FIVE-YEAR SURVIVAL RATES FOR PATIENTS WITH REGULAR CURATIVE EXCISIONS OF ADENOCARCINOMA OF THE COLON (1940-1950)

	SIGMOID COLON	DESCENDING COLON	SPLENIC FLEXURE	TRANSVERSE COLON	HEPATIC FLEXURE	ASCENDING COLON	CECUM	TOTAL COLON
Dukes A								
Number of cases	30	12	1	9	1	5	29	87
Hospital deaths	2	1	0	0	0	0	2	5
5-yr. survivors	22	8	1	9	1	4	23	68
Per cent 5-yr. survival	78.5	73	100	100	100	80	85	83
Dukes B								
Number of cases	14	6	0	7	1	1	9	38
Hospital deaths	2	0	0	1	0	0	0	3
5-yr. survivors	11	4	0	4	1	1	3	24
Per cent 5-yr. survival	92	67	0	67	100	100	33	68.5
Dukes C								
Number of cases	32	5	2	5	3	6	21	74
Hospital deaths	1	0	0	0	0	0	2	3
5-yr. survivors	13	1	0	5	2	3	8	32
Per cent 5-yr. survival	42	20	0	100	67	50	42	45
Total								
Number of cases	76	23	3	21	5	12	59	199
Hospital deaths	5	1	0	1	0	0	4	11
5-yr. survivors	46	13	1	18	4	8	34	124
Per cent 5-yr. survival	65	59	33	90	80	67	62	66

TABLE X. 5-YEAR CANCER-FREE SURVIVAL RATE IN ALL CASES OF ADENOCARCINOMA OF THE COLON (1940-1950)

	SIGMOID COLON	DESCENDING COLON	SPLENIC FLEXURE	TRANSVERSE COLON	HEPATIC FLEXURE	ASCENDING COLON	CECUM	TOTAL COLON
Number of cases	160	35	12	46	13	24	114	404
5-year cancer-free survivors	47	11	1	20	4	8	38	129
Survival rate	33%	37%	8%	46%	31%	33%	35%	32%

TABLE XI. SURVIVAL IN CASES OF ADENOCARCINOMA OF THE COLON AND RECTUM NOT SUBJECTED TO CURATIVE EXCISION
(1940-1950, Palliative Excisions; 1940-1955, Others)

	NUMBER OF CASES	LEFT HOSPITAL ALIVE		MEDIAN SURVIVAL (MONTHS)	NUMBER OF PATIENTS REMAINING ALIVE											
					6 MONTHS		1 YEAR		2 YEARS		3 YEARS		4 YEARS		5 YEARS	
		NUMBER	PER CENT		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Palliative Excision																
Colon	56	53	95	11	37	66	15	27	6	11	3	5	1	2	0	0
Rectum	55	53	95	12	40	73	28	49	11	20	5	9	4	7	1	2
Colostomy																
Colon	41	29	71	3	14	34	6	15	1	2.5	1	2.5	0	0	0	0
Rectum	105	87	83	5	44	42	22	21	5	5	2	2	0	0	0	0
Catheter enterostomy or cecostomy																
Colon	7	1	14	0	0	0	0	0	0	0	0	0	0	0	0	0
Rectum	–															
Ileostomy																
Colon	3	1	33	0	0	0	0	0	0	0	0	0	0	0	0	0
Rectum	–															
Bypass procedure																
Colon	7	6	86	4	3	43	1	14	0	0	0	0	0	0	0	0
Rectum	1	1	100	–	1	100	1	100	1	100	1	100	1	100	0	0
Laparotomy only																
Colon	14	11	79	2	3	21	1	7	0	0	0	0	0	0	0	0
Rectum	6	6	100	9	4	67	0	0	0	0	0	0	0	0	0	0
Inoperable																
Colon	10	10	100	2	0	0	0	0	0	0	0	0	0	0	0	0
Rectum	14	14	100	3	3	21	2	14	1	7	0	0	0	0	0	0
Refused treatment																
Colon	4	4	100	–	2	50	2	50	1	25	1	25	1	25	0	0
Rectum	16	16	100	6.5	8	50	4	25	3	19	1	6	0	0	0	0

associated with a postoperative survival of almost 11 months and colostomy with 3 months, of 10 cases with catheter enterostomy, cecostomy, or ileostomy, only 2 patients were able to leave the hospital alive and none survived 6 months.

Operative or hospital mortality (death before leaving the hospital or within 30 days of operation) was 4.88 per cent for the 574 regular excisions for large bowel lesions. A 5.4 per cent rate was present for colon cancer, and 4.4 per cent for rectal cancer.

Thirty-two patients were seen with lesions present in more than one anatomic site in the large bowel. Patients with 2 or more lesions in the same area of the bowel are not included.

Of the 32 patients, 29 underwent excisions. Of these, 20 had an excision designed for cure (Table XII). When operative deaths are deducted, the 5-year survival rate was 35 per cent in these cases (Table XIII).

TABLE XII. LESIONS AT 2 OR MORE SITES IN 32 PATIENTS WITH ADENOCARCINOMA OF THE LARGE BOWEL (1940-1950)

	NUMBER OF CASES
Multiple lesions, one operation	20
Curative excisions	13
Palliative excisions	7
Multiple lesions, 2 or more operations	9
Curative excisions	7
Palliative excisions	2
Lesions excised — total cases	29
Lesions not excised	3
Inoperable	2
Bypass procedure	1
Total cases	32

TABLE XIII. CURATIVE EXCISIONS FOR LESIONS AT 2 OR MORE SITES IN 20 PATIENTS WITH ADENOCARCINOMA OF THE LARGE BOWEL (1940-1950)

	NUMBER OF CASES				OPERATIVE DEATHS	5-YR. SURVIVORS	
	TOTAL	2 LESIONS	3 LESIONS	4 LESIONS		NUMBER	PER CENT
One operation	13	9	3	1	3	2	20
Two or more operations	7	7	0	0	3	3	75
Total	20	16	3	1	6	5	35

Study was made correlating patients' ages at the time of curative excisions with the likelihood of 5-year postoperative survival (Table XIV). When the average for the entire colon is considered, the most favorable prognosis was related to the 45 to 54 year age group; 63 per cent survived 5 years. The transverse colon was the only area of the large bowel which was associated with 5-year postoperative survival of any patient of 80 years or over at the time of operation; 2 of the 3 cases had a 5-year postoperative survival.

TABLE XIV. AGE AT OPERATION AND 5-YEAR SURVIVAL RATE FOR PATIENTS WITH CURATIVE EXCISIONS FOR ADENOCARCINOMA OF THE LARGE BOWEL
(1940-1950)

AGE AT OPERATION (YEARS)	LEFT COLON			RIGHT COLON			TRANSVERSE COLON			RECTUM		
		5-YR. SURVIVORS			5-YR. SURVIVORS			5-YR. SURVIVORS			5-YR. SURVIVORS	
	NUMBER OF CASES	NUMBER	PER CENT	NUMBER OF CASES	NUMBER	PER CENT	NUMBER OF CASES	NUMBER	PER CENT	NUMBER OF CASES	NUMBER	PER CENT
20-44	12	5	42	7	3	43	5	5	100	22	11	50
45-54	20	14	70	19	10	53	5	5	100	45	23	51
55-64	40	20	50	23	14	61	5	4	80	97	49	50.5
65-74	42	23	55	34	18	53	8	3	37.5	86	35	41
75-79	8	4	50	13	7	54	1	0	0	18	7	38
80-89	6	0	0	3	0	0	3	2	67	11	0	0

DISCUSSION

The composition of the present series of cases would appear to approximate others of comparable size which have been seen at large teaching hospitals.[12, 19, 22] The median age of the patients (63 years), however, is several years greater than that usually reported and 10 to 15 years more than cases reported earlier. The 98 per cent operative rate for the over-all 1940 through 1955 group[13-15]—even a bit improved from the 1940 through 1950 97.5 per cent rate—is worthy of note. The resection rate showed substantial improvement, especially for the colon cases (87 per cent, 1940 through 1955).

Classification of the anatomic locations of the 1,298 single lesions corresponds to the classical picture.[24] The observation that one-third to one-half of large bowel lesions are located in sites which permit diagnosis by simple digital examination receives confirmation; 36.9 per cent of lesions were located in the true rectum and another 16.5 per cent in the rectosigmoid region.[4, 16] Of interest is the fact that 15 patients (3 per cent) with rectal lesions actually made their own diagnosis by self-palpation of the lesion.[11]

The relatively high figure (77 per cent) for the portion of excisions which were performed for cure should be noted when evaluating strictness of criteria for classification of cases as palliative. The herein observed resection rates plus the high rate of excisions performed for cure are worthy of note when assessing validity of cure rates and the concept of curative excisions.

The 5-year survival rates computed for patients with lesions at each of the anatomic sites of the large bowel (Tables VIII and IX) are based on sufficient cases to allow further classification by stage of disease. When survival rates for regular curative excisions are arranged in a decreasing order of frequency by anatomic sites, the following situation is present: transverse colon (90 per cent), ascending colon (67 per cent), entire colon (66 per cent), sigmoid colon (65 per cent), cecum (62 per cent), total large bowel (56.4 per cent), and rectum (49 per cent). The most easily diagnosed lesions, rectal tumors, had the least favorable prognosis. Lesions present in an area often considered unfavorable for early diagnosis—the transverse colon—actually had an excellent prognosis.

Of interest is the differing ratio between prognosis following excision of Dukes A and C lesions for the various sites in the bowel. What may be termed the "C/A" ratio, the ratio of 5-year survival rate for Dukes C lesions to that for Dukes A lesions, indicates the following: transverse (1.0), ascending (0.625), entire colon (0.54), sigmoid (0.53), cecum (0.49), total large bowel (0.44), and rectum (0.34).[8] This ratio would appear to be somewhat indicative of the gravity associated with spread of malignancy in each of these locations; the smaller the ratio, the graver the consequences. Patients with lesions of the transverse colon again had the most favorable outlook, and those with rectal lesions, one of the least favorable.[20]

Of interest are the results of enlarged excisions performed for cure (Table VIII). These compare rather well with results following regular excisions of Dukes C lesions. That is, tailoring the size of the operation to the

size of the grossly evident disease spread appears to have been associated with substantial success, when these results are compared with accomplishments of regular curative excisions for Dukes C lesions. These observations, based on follow-up study of a substantial number of cases, add evidence that present-day surgeons need not be bound by yesterday's dogmas. The employment of large operations for large cancers and smaller operations for small cancers would, under certain circumstances, appear altogether fitting and proper.[1, 3, 23] Further indication of the validity of the principle may be noted in the more detailed report of rectal cancer in the 1940 through 1950 group. Small procedures (those other than abdominoperineal) when employed in the treatment of patients with Dukes A rectal tumors were as successful as were large operations (abdominoperineal), but Dukes C lesions appeared to necessitate the larger operation (abdominoperineal) for any considerable success.[9, 18]

Survival statistics following palliative procedures and for other cases not operated upon for cure emphasize that in the instances in which palliative excision could be done, substantial 1- or 2-year survivals were achieved. Colostomy was associated with about one-half that rate. Interestingly enough, patients who refused treatment appear to have survived almost as long as patients who underwent palliative excision. Catheter enterostomy, cecostomy, or ileostomy, however, were associated with palliation of—at most—a few weeks' duration.[5]

Correlation, in a statistically significant number of cases, of age at time of curative excision with 5-year postoperative survival rate offered evidence bearing on several currently debated questions. For example, this study lends no support to the contention that bowel malignancies in younger patients (less than 44 years of age) are associated with an overwhelmingly poor prognosis; the figures presented here indicate that prognosis is relatively good. Another oft-repeated aphorism—that advanced age at operation has little bearing on prognosis—appears not to apply to patients 80 years or older, except those few with lesions of the transverse colon; no patient with an adenocarcinoma of the large bowel (other than transverse colon) achieved 5-year post-operative survival.[6, 27]

SUMMARY AND CONCLUSIONS

1. Study of 1,340 cases with adenocarcinoma of the large bowel was made. Follow-up of cases was 100 per cent. The general composition of the group indicated that patients were somewhat older than in the usually reported series. Operative, resection, and survival rates, however, compare favorably.

2. Two-thirds of the patients with carcinoma of the colon died of their disease without 5-year survival (32 per cent survival) (Table X). When patients underwent excisions for cure, however, about two-thirds of those with colon cancers and one-half of those with rectal cancers survived 5 years.

3. When patients with Dukes A lesions are considered, 83 per cent of those with colon lesions survived 5 years—including 100 per cent with lesions of the splenic flexure, hepatic flexure, and transverse colon.

4. The most favorable prognosis following excision for cure was associated with transverse colon lesions (90 per cent 5-year postoperative survival); the least favorable, with rectal lesions (49 per cent).

5. The popular reluctance against employment of larger operations for large cancers receives little support; enlarged excisions allowed substantial survival of patients who may otherwise have been inoperable for cure.

6. Curative excisions in the younger age group (44 years or younger) were followed by acceptable survival rates. This was not noted in patients 80 years or older, except transverse colon cases.

7. Palliative excisions were associated with measurable palliation, as were colostomies performed without resection; cecostomy, catheter enterostomy, and ileostomy, however, were not.

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POSTOPERATIVE (ADYNAMIC) ILEUS

Its Prevention by Ambenonium Chloride

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POSTOPERATIVE (adynamic) ileus is a common sequela of major surgical operations, especially intra-abdominal procedures.[5] During the first days of the postoperative period there is a temporary paralysis of the intestinal tract. This change in the bowel activity can be detected easily with a stethoscope placed upon the abdomen.[6]

The course of the postoperative ileus varies. Some patients expel flatus and recover in a few days. In others there is accumulation of gas and fluid, and abdominal distention appears. Therefore, either the intestinal paralysis is not accompanied by distention but is diagnosed by auscultation (simple ileus), or the ileus is accompanied by abdominal distention. It is well recognized that simple ileus occurs in practically all cases of intra-abdominal surgery.

This classification of simple ileus and abdominal distention is important from the viewpoint of its treatment. While simple ileus does not require a strict treatment, prophylactic measures to prevent distention can be beneficial. In ileus accompanied by distention, active therapeutic measures are mandatory.

Unfortunately there are some authorities who believe ileus to be a matter of little or no importance. It is true that not all postoperative cases progress to severe abdominal distention, but it is impossible to foresee which patient will develop distention and which will not. Moreover, it is accepted that a prophylactic treatment is always more effective and requires less medical attention than a therapeutic one, and the prophylactic method could prevent progression to abdominal distention, and can decrease the discomfort of the patient with simple ileus.

While intubation has been accepted as an effective treatment for the patient with distention,[5] only a few authors consider this procedure as a practical prophylactic measure. Because 70 per cent of the gas in distention has been swallowed, theoretically speaking, a gastric tube with constant suction appears to be an effective measure.[4] In actual practice this is not so, and besides it produces a host of undesirable side effects (irritation of the throat, of the nares and so forth). Intestinal intubation should be a better procedure, but also, for obvious reasons, is not a practical method. Among other disadvantages, intestinal intubation carries a high incidence (14.3 per cent) of respiratory tract complications.[6]

A simple method of prevention (and treatment) of postoperative ileus is by means of drugs which stimulate peristalsis. Opinions about the efficacy of

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these agents vary considerably, and even those authorities who considered them favorably thought that such drugs were too toxic to be used in therapeutically adequate dosage.

A new drug, ambenonium chloride, has been found effective both prophylactically and therapeutically.[1-3]

This report deals with the results obtained with ambenonium chloride used prophylactically in 400 cases over a period of 3 years.

MATERIALS AND METHOD

Two groups of patients submitted to intra-abdominal surgery were used in this study. One received treatment with ambenonium chloride. The other received no ambenonium chloride. Cases of the first or second group that progressed to distention were considered failures and were treated accordingly. Due to difference of size of the groups, results were analyzed by statistical methods.

All cases of the trial group receive 1 c.c. of a 1:16,000 solution of ambenonium chloride,* at 4-hour intervals, day and night. Treatment was started as soon as the patient was returned from the operation room and was continued until the attending surgeon believed that normal peristalsis was reinstated.

RESULTS

A résumé of the 400 cases treated prophylactically with ambenonium chloride appears in Table I.

TABLE I

	NUMBER OF CASES	NUMBER OF DOSES*	DAYS OF TREATMENT*
Gastrointestinal operations	199	6-111	2-19
Hepatic operations	35	3-5	2-8
Other operations	166	3-44	2-12

*Maximum and minimum.

The gastrointestinal operations include mainly gastrectomies, acute appendectomies, intestinal anastomosis, suture, and epiploplasty (in peptic ulcer).

The hepatic group consisted mainly of cholecystectomies.

The "other operations" group includes principally herniorrhaphies and simple laparotomies.

The four largest groups of operations were: herniorrhaphies, gastrectomies, appendectomies, and cholecystectomies, in decreasing incidence. These four operations account for 76 per cent of the total.

All postoperative patients receiving ambenonium chloride except two did not become distended. This represents 0.5 per cent failure as compared with 7.14 failure in the control group. Since the two groups were unequal in number, statistical methods were used to demonstrate the "credibility." The X^2 was equal to 17.

Very few slight reactions were encountered in the 400 treated cases, after more than 7,800 injections; approximately 0.14 per cent had reactions. These

*Prepared by Winthrop Laboratories.

reactions were principally a sensation of warmth, thick tongue, and so forth. Treatment was discontinued in one patient; an asthma attack appeared after the injection of ambenonium chloride.

Our personnel, well trained in using other peristalsis-stimulating drugs, found that the number and degree of reactions produced by ambenonium chloride were less than the ones produced by neostigmine.

COMMENT

In the analysis of cases of ileus, the natural difficulties of a study of this kind must be kept in mind. Certain publications did not distinguish between simple ileus (as defined here) a common, benign sequela of surgery, and ileus with distention, a less common but severe clinical form of ileus. Other authors have selected initial flatus as the end point. As this is a subjective sign, the results depend somewhat on the cooperation of the patient, as well as our ability to supply clear-cut instructions.

We have adopted distention as our end point. This is a subjective symptom that not only could be appreciated by attending personnel (nurses, internists, associates) but can be measured roughly. Besides, when distention is severe, respiratory embarrassment produces dyspnea or, better, polydyspnea. This polydyspnea can be appreciated quantitatively.

Since practically 99 per cent of intra-abdominal operations produce simple ileus, which itself is not dangerous, our idea was to prevent progression from simple ileus normally appearing in intra-abdominal cases to ileus accompanied by distention.

In the past we have had ample experience with other peristalsis-stimulating agents, mainly with neostigmine. While this product was fairly satisfactory, it produced a high percentage of failures and a higher percentage of reactions. This is clearly explained when it is known that the "adequate" dose of neostigmine is near the toxic one.[7] We have had several cases in which neostigmine failed but the patient recovered (that is, the distention disappeared) under treatment with ambenonium chloride.

It is our clinical impression based on these 400 patients who received more than 7,800 injections that prophylactic treatment with ambenonium chloride seems to be more effective than the same treatment with neostigmine. This belief is based on two facts: (a) In the average case, ambenonium chloride is more powerful than neostigmine. This is deducted from a series of more than 20 cases in which neostigmine was ineffective and ambenonium was effective. (b) Ambenonium chloride produces a lower incidence of secondary reactions. This last statement has been substantiated by other investigators working in different clinical projects using ambenonium chloride for other conditions.

SUMMARY

Four hundred surgical cases were treated prophylactically with ambenonium chloride to prevent the production of abdominal distention. The dosage used in the majority of the cases was 1 c.c. of 1:16,000 solution of ambenonium chloride every 4 hours.

In 398 of 400 cases, abdominal distention was prevented.

Results in this group were compared statistically with a control group.

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ACUTE EPIPLOIC APPENDAGITIS

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EPIPLOIC appendagitis should no longer be considered a surgical or pathologic rarity. With the more improved methods of diagnosis and better training of surgeons in the detection of pathologic entities, it has been demonstrated that involvement of the epiploic appendages with pathology occurs more frequently than was commonly suspected. The condition is rarely given preoperative consideration. It can mimic many of the acute intra-abdominal inflammatory syndromes and, in addition, can produce mechanical intestinal obstruction. It may also present as an incarcerated hernia, simulate an intra-abdominal neoplasm, and occur as intraperitoneal loose bodies.

Although the condition cannot be classified with acute appendicitis as a highly treacherous disease, it has been directly responsible for fatalities and has caused severe surgical complications.

HISTORY

The condition was first described by Vesalius,[11] in 1543. In 1703 Littre[6] found a free hard oval body, measuring 2.5 cm. in length, in the abdominal cavity during the dissection of a cadaver. Similar bodies were reported by Schede[10] and Cruveilhier.[2] The epiploic appendages assumed surgical significance when Virchow,[12] in 1853 suggested their detachment as a source of intraperitoneal loose bodies. By 1900, sporadic case reports had appeared describing torsion of the appendages with or without associated symptoms. Cruveilhier[2] first described a case of intestinal obstruction in which an epiploic appendage had acted as a band; Reidel,[9] in 1905, described torsion of an epiploic appendage in a femoral sac.

A review in 1936 by Fiske[4] disclosed 21 cases of diseased epiploic appendages requiring operation. Infarction and inflammation of the appendages without torsion were present in several of these cases. In 1942, Giffin and associates[5] added 10 cases of symptomatic disease of the appendages to the 49 previously reported cases. It was their impression that obesity was a factor in the genesis of the condition. Fieber and Forman,[3] in 1953, reported records of 105 cases of pathologic epiploic appendages in the literature and added 3 more cases of their own.

Search of the available literature by Lynn and colleagues[7] disclosed a total of 156 reported cases of diseased epiploic appendages requiring surgical intervention. Inflammation of the appendage was present in 109 cases, whereas intestinal obstruction was present in 13 cases. The appendages presented as hernias in the remaining 34 cases.

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PATHOLOGY

The epiploic appendages are fat-filled, serosa-covered appendages occurring on the large intestine, including the appendix but excluding the rectum. The enveloped fat is a continuation of the subserosal fat of the intestinal wall. Their appearance has been noted as early as the fifth month of fetal life, although appreciable size is not attained until adulthood. Approximately 100 in number, they are related intimately to the longitudinal bands of the colon, usually appearing in 2 rows. Their average length is 3 cm. but they have been reported to be as long as 15 cm. Blood is supplied by small branches of the circular artery that vascularizes the adjacent segment of colon. Subserosal lymphatic channels may terminate in a lymph node within an appendage or loop through its base en route to mesenteric nodes. Diverticula have been encountered within the substance or epiploic appendages, and this relationship has been considered to be due to the proximity of the appendages to the sites where the large vessels enter the intestinal wall.

Functionally, the epiploic appendages have been described as representing a protective and defensive mechanism similar to the great omentum. However, the small surface area and limited vascularity reduce this capacity to a minimum. It also has been postulated that they might act as a protective cushion during peristalsis or, as Pines and associates[8] suggested, a depot for the redundant adjacent circular vessel when the colon is collapsed.

From a pathologic standpoint, the findings are similar regardless of the location of the involved appendage. In the acute phase, the appendages have been reported as showing varying degrees of hemorrhagic infarction, gangrene, and suppuration. Fibrosis, hyalinization, cystic changes, and calcareous degeneration have supervened when the process is chronic.

The pathologic conditions, as encountered in 102 cases by Fieber,[3] may be divided into six categories: (1) torsion, 31.4 per cent; (2) thrombosis and infarction, 15.6 per cent; (3) gangrene, 19.7 per cent; (4) acute inflammation and suppuration, 18.6 per cent; (5) chronic inflammation (replacement by fibrous connective tissue, hyalinization, and calcareous degeneration), 13.7 per cent; and (6) intussusception, 1.0 per cent.

Although the actual twist is only occasionally demonstrated at surgery, it is generally accepted that torsion of the pedicle is an important factor in compromising or strangulating the blood supply.[8] The cause of torsion is unknown, but numerous possibilities can be postulated to initiate the chain of events, such as: (1) sudden rotation of the body or violent exertion; (2) congenital malformation of an appendix epiploica so that the base is narrower and freer to rotate; (3) anatomic arrangement of vessels such that the veins are longer, more tortuous, and hence more likely to twist around an artery and produce venous occlusion (this process may be augmented by the physiologic splanchnic dilatation with its characteristic mesenteric venous engorgement during the process of digestion; during this phase the distal dependent portion of the appendix epiploica

is heavier and contains more fat and venous blood than does the proximal portion); or (4) the appendix epiploica, heavy with fat, as it swings freely from the taenia making a likely candidate for torsion (it has been noted that torsion is more likely to occur in well-nourished persons).

Torsion of an intrahernial appendix epiploica can be explained by the fact that the appendage twists on entrance into the hernial ring during a period of coughing or straining. The tip of the appendix epiploica follows along the wall of the sac, and its base or pedicle remains more or less fixed.

There are all degrees of torsion. A sudden torsion is followed by subperitoneal hemorrhage, with its attendant symptoms, slight or severe, whereas an insidious twisting may be productive of chronic inflammatory changes, with its own train of symptoms resulting in ischemic fat necrosis and calcification. The necrotic mass may be free in the abdomen or attached to the bowel wall, causing paroxysmal pain. Aseptic gangrene or primary thrombosis of an epiploic vessel is the outcome of appendiceal torsion in the absence of secondary infection. After organization of the devascularized tissue takes place, it may separate at the line of demarcation and pass off into the general peritoneal cavity as a loose body.

An explanation of primary inflammatory disease of the appendix epiploica with or without frank suppuration and in absence of torsion is offered. Lymph node structures within the appendix epiploica may account for it. The frequency of diverticula in relation to appendicitis epiploica has been noted. The relationship between diverticula and appendicitis epiploica seems to be due to the fact that these fatty masses are situated either directly on or close to points where the larger vessels enter the intestinal wall. Conceivably, bacteria may infiltrate through the wall of a diverticulum into an appendix epiploica. Not infrequently, in cases of acute diverticulitis, involvement of one or more appendix epiploica is noted, but this condition and its implications belong to the pathology of diverticulitis. This also applies to those appendices that have become secondarily infected from a vermiform appendix. A case of appendicitis epiploica occurring in conjunction with regional ileitis has been reported.

Abscess formation and even general peritonitis may result either from inflammation or from torsion. More frequently, intestinal obstruction occurs in connection with inflammatory adhesive bands either between appendages or from one or other organ or from the parietes. A common cause of the obstruction is the adhesion of a pair of appendices across the antimesenteric surface of the bowel, causing narrowing of the lumen. In addition, incarceration of the cecal or sigmoidal appendix in a hernial sac may so angulate the bowel at the mouth of the sac as to give rise to actual obstruction.

SIGNS AND SYMPTOMS

The signs and symptoms of epiploic appendagitis are most often misleading. They will vary in individual cases and will of course depend on the anatomic location of the lesion. In the reported cases the acute symptoms lasted less than

one week (Fieber[3]) in 70 per cent of the cases, in 11 per cent they lasted from 1 to 4 weeks, and in the remaining 19 per cent symptoms lasted more than one month. In our group of cases the symptoms lasted less than a week.

Abdominal pain is the chief presenting symptom in all cases. It may be sudden in onset and described as dull, sharp, or even colicky. The site of the pain varies with the location of the pathology and about one-half of the cases refer to the right lower quadrant with pain relative to the position of the sigmoid and cecum. The pain may be centrally located or spread centrally and not infrequently to the left side. The next most common site for pain is the left lower quadrant.

Nausea and vomiting occur in about one-quarter of the cases. The appetite and bowels are usually unaffected. Temperature and pulse elevations and leukocytosis occur with the progression of pathology in the appendage.

Abdominal examination reveals the presence of signs of peritoneal irritation at the site of pathology. There is rarely generalized rigidity but definite guarding and spasm are present in the majority of cases. Pin-point tenderness is often elicited over the region of the involved appendage. A palpable mass is encountered in a small percentage of cases.

DIFFERENTIAL DIAGNOSIS

Acute abdominal pain, with or without an associated palpable mass, is the most significant symptom produced by an acute epiploic appendagitis. Acute appendicitis is the usual preoperative diagnosis if the symptoms and signs are localized in the right lower quadrant. Sigmoid diverticulitis is considered if the signs are in the left lower quadrant. Three-quarters of the cases reported occurred in either the cecum or sigmoid and the remainder were distributed throughout the remaining colon excluding the rectum.

A definite preoperative distinction between acute epiploic appendagitis and acute vermiform appendicitis can only be speculative. However, several differences are worthy of consideration. Epiploic appendagitis is usually a disease of middle age and the patients are obese. The pain, at the onset, almost always is localized at the site of pathology whereas with appendicitis it is most often diffuse and generalized throughout the abdomen. When a sigmoidal appendage is involved, shifting of the pain and tenderness across the lower abdomen may occur as the patient changes position. Anorexia, nausea, vomiting, and constipation are more likely to occur with appendicitis, and such patients appear more toxic and show more pronounced febrile and leukocytic response.

Another condition worthy of consideration in patients with acute symptoms and signs in the right lower quadrant is the presence of cecal diverticulitis since this condition occurs in approximately 2 per cent of all cases of acute diverticulitis of the entire colon. Again, the preoperative distinction can only be tentative.

CASE REPORT

Four cases with symptoms and signs necessitating surgical intervention are herewith presented.

CASE 1.—P. B. (077168), a 22-year-old white man, was admitted for the first time to St. Vincent's Hospital in New York City, March 16, 1959, complaining of sharp right lower quadrant pain of 3 days' duration. The pain remained localized to the right lower quadrant but had become more pronounced on the day of admission. There was no nausea or vomiting and the patient had not had any similar experience in the past. There were no urinary complaints.

Physical examination revealed an obese young white man weighing 238 pounds with a temperature of 99° F., pulse rate of 80, and a white blood count of 12,800 with 80 per cent neutrophils. Urinalysis was negative. He appeared acutely ill.

Abdominal examination revealed the presence of pin-point tenderness over the region of the appendix with definite guarding. The patient was advised to have an emergency exploratory laparotomy for an inflammatory condition in the right lower quadrant. The preoperative diagnosis was not definite. At operation an infarcted epiploic appendage was found on the anterior cecal wall close to the base of the vermiform appendix. Both the involved appendage and appendix were removed and the patient made an uneventful recovery.

Pathologic report: Acute panniculitis with necrosis of an appendage epiploica, and periappendicitis of vermiform appendix.

Comment: This was a young obese man who gave a suspicious history of an inflammatory condition in the right lower quadrant other than that of an acute appendicitis. The absence of nausea or vomiting was significant and prompted us to venture the diagnosis of acute cecal diverticulitis and should have also suggested the possibility of acute epiploic appendagitis. Immediate surgery was definitely indicated and was performed in order to avoid possible complications of such conditions with conservative therapy.

CASE 2.—E. L. (E 3982), a 46-year-old white obese woman, was admitted to the hospital on April 20, 1954, with the history of indefinite abdominal discomfort for the previous 3 months. In the 48 hours prior to admission she had experienced acute left lower quadrant pain with no nausea or vomiting.

Physical examination revealed an obese young white woman with a temperature of 100° F., pulse rate of 85, and a white blood count of 14,000 with 75 per cent neutrophils. Urinalysis was negative. She appeared acutely ill.

On abdominal examination a mass measuring about 8 cm. in diameter could be palpated in the left lower quadrant. It was tender and appeared to be fixed. Sigmoidoscopy was negative.

Exploratory laparotomy was performed the day after admission with the preoperative diagnosis of intra-abdominal abscess secondary to diverticulitis of the sigmoid colon. At operation a 4 by 2.5 cm. twisted and inflamed epiploic appendange was found in the mid-sigmoid colon with a mass of omentum adherent about it. The appendage had a vascular stalk that measured 3 cm. in length. There was no evidence of a diverticulum. The involved appendage was excised without difficulty after separating the omental covering about it. The patient made an uneventful recovery.

Pathologic report: Chronic inflammation and localized hemorrhagic necrosis of an epiploic appendage.

Comment: This patient presented a problem for differential diagnosis. The history and the presence of a mass in the left lower quadrant would naturally lead us to believe that the condition was probably one of sigmoid diverticulitis with abscess formation or possibly a neoplasm with secondary inflammation.

The presence of the mass of omentum about the appendage is consistent with the long history of abdominal discomfort. She undoubtedly had had similar previous acute episodes with the omentum attempting to seal off the process over an extended period of time. The last acute episode was of 48 hours' duration.

CASE 3.—P. C. (C77156), a 59-year-old white man, was admitted to St. Vincent's Hospital, New York City, with history of painful left inguinal hernia. He stated that he had had the hernia for 10 years but that 36 hours before admission it became quite tender and somewhat swollen. He was not nauseated and did not vomit.

Physical examination revealed an adult white obese man with a temperature of 100° F., pulse rate of 74, and a white blood count of 11,000 with 76 per cent neutrophils.

Abdominal examination was essentially negative, except for a mass in the right inguinal region which was quite tender and not reducible. A diagnosis of incarcerated inguinal hernia was made and an emergency operation performed. A gangrenous epiploic appendage from the sigmoid wall was found adherent to the apex of the hernial sac. There was a moderate amount of fluid in the sac. The appendage was excised and the hernia repaired. The patient made an uneventful recovery.

Comment: This patient presents another complication of acute epiploic appendagitis in an individual with a hernia. Although the preoperative diagnosis was incorrect, the decision to operate immediately was indicated and justified by what was found at operation.

CASE 4.—E. D. (C80134), a 38-year-old white woman, was admitted to St. Vincent's Hospital, New York City, on March 30, 1952, with a history of intermittent lower abdominal pain for several years. Prior to this admission the pain, which was dull in character and more localized to the left lower quadrant, had become more severe and persistent. She was not nauseated nor did she vomit. There were no urinary symptoms.

Physical examination revealed an obese young woman with a normal temperature, pulse rate of 74, and a normal white blood count.

Abdominal examination revealed the presence of a mass in the lower mid-abdomen with some definite tenderness and guarding in the left lower quadrant.

Vaginal examination revealed the presence of a large fibroid uterus.

Preoperatively it was believed that the tenderness of the left lower quadrant might possibly be due to a twisted pedunculated fibroid; however, at operation a hard, indurated, acutely inflamed mass was found on the antimesenteric border of the mid-portion of the sigmoid, and it was adherent to the left portion of the uterine body. On further examination of the mass it was found to be a strangulated epiploic appendage. It was removed without difficulty and then a hysterectomy was performed. She made an uneventful recovery.

Comment: In this patient the presence of numerous fibroids made us suspect a twisted pedunculated fibroid as the cause of the acute abdominal distress. Again, this is another example of how an appendagitis can mimic other more common and usually suspected conditions in the abdomen.

SUMMARY AND CONCLUSION

1. Four cases of acute epiploic appendagitis are reported.

2. The condition should be entertained in the differential diagnosis of cases with right or left lower quadrant pain if nausea and vomiting are not present.

3. The treatment is surgical, even if the diagnosis is made preoperatively, in order to avoid the possible complications of an acute progressive disease process.

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INTESTINAL LIPOMATOSIS

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MULTIPLE intestinal lipomas are rare. Nevertheless, they represent a problem in diagnosis and surgical management.

Since the first reported intestinal lipoma in 1747,[3] numerous case reports of solitary lipomas and occasional reports of multiple lipomas have appeared. Stetten[23] recorded 2 patients with solitary lipomas of the intestinal tract in 1909. Kirshbaum[13] described 9 patients in whom a solitary lipoma was found in the small bowel. Mayo and Greiss[15] reported 19 patients with solitary colonic lipomas. Henderson, Harris, and Parker[10] cited 5 others. Warren and Brandenburg[25] reviewed 11 patients with intestinal lipomas. One of these had several lipomas in the jejunum. The remainder had a solitary lipoma. Comfort[4] reviewed 181 patients with submucous intestinal lipomas and found 2 patients with multiple lipomas. In one patient, numerous lipomas involved the descending and sigmoid colon and, in another, 90 submucous lipomas were found at autopsy to be distributed throughout the small bowel. Smith and Mayo,[22] in a review of 67 patients with lipomas of the small bowel, reported one patient in whom multiple lipomas involving the small bowel were found at autopsy. Schottenfeld[21] mentioned Francini's case of multiple submucous lipomas of the ileum discovered incidentally during a laparotomy for gastric carcinoma. Findley and Thompson[8] reported a patient with 12 lipomas in a 21 cm. segment of ileum.

Intestinal lipomatosis has not previously been reported as an operative finding.

CASE REPORT

H. D., a 60-year-old Negro woman, was admitted to the Philadelphia General Hospital on March 23, 1959. Her first admission occurred in 1952 at which time she complained of intermittent abdominal pain and vomiting. Barium x-rays of the gastrointestinal tract were not performed. Because of a large pelvic mass, a laparotomy and total hysterectomy were performed. A large benign right ovarian cyst and multiple uterine fibroids were found. No mention was made of intestinal tumor. She was next admitted to the surgical service of this hospital in April, 1953, because of copious bright red rectal bleeding. A barium enema at that time revealed a polypoid lesion of the terminal ileum with ileocecal intussusception. The patient refused laparotomy and was discharged to the outpatient department. She did not return until March, 1959. At that time, she complained of intermittent lower abdominal pains of approximately 8 months' duration. The pains were cramping in nature and radiated from the periumbilical area to the right lower and right upper abdominal

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quadrants. They were relieved by the passage of flatus or feces, but generally subsided spontaneously. She had also noted in recent weeks the onset of nausea and vomiting. She had noted increasing constipation during the preceding year.

No other members of her family had similar complaints.

Physical examination revealed a moderately obese Negro woman. No melanotic spots were noted on the skin or mucous membranes. The blood pressure was 168/80 mm. Hg. The abdomen was not distended. A firm, movable, slightly tender fusiform mass was palpable in the right lower quadrant in the area of the cecum. Peristalsis was normal.

Proctoscopic examination revealed a smooth polypoid lesion in the sigmoid colon approximately 28 cm. above the anus about 3 cm. above the end of the proctoscope. A barium enema examination revealed an ileocecal intussusception, which was partially reduced by the influx of barium. It was further noted that the intussusception recurred with evacuation of the barium. Numerous other polpoid lesions were identified throughout the colon (Fig. 1). In addition, this study revealed that the mucosa of the terminal ileum was irregular in outline suggesting a neoplastic disease. Other filling defects were noted throughout the entire large bowel.

A small intestinal barium x-ray revealed numerous polypoid masses throughout the small intestine from the second part of the duodenum to the terminal ileum. The terminal 2 feet of ileum appeared to be almost entirely filled with polypoid lesions (Fig. 2).

The hemoglobin was 12.1 Gm. The white blood count was 8,200. Serum cholesterol was 242 mg. per cent with 71 per cent esters.

Operation.—On April 1, 1959, the patient was explored with the preoperative diagnosis of multiple polyposis. Examination of the small intestine revealed numerous intraluminal, polypoid, soft, movable tumors. These varied in size from a few millimeters to 5 cm. in diameter. They were most numerous in the terminal ileum where they occurred every 3 to 4 inches as compared to the proximal jejunum where they occurred at 8- to 10-inch intervals. The mesentery of the small bowel contained no primary or metastatic masses. The distal 3 feet of ileum was found intussuscepted into the right colon as far as the proximal transverse colon. Palpation of the transverse, descending, and sigmoid colons revealed numerous similar masses. Palpation of the duodenum revealed a small soft polyp in the first portion of the duodenum just below the pylorus, and a slightly larger polyp measuring 1 cm. by 1 cm. at the junction of the second and third portions of the duodenum.

Two areas of ileoileal intussusception were noted and both were reduced easily. In each, a large polypoid intraluminal mass was palpated at the intussuscepting point. When the more proximal ileal intussusception was reduced, the intussusception was seen to recur. A resection of the ileocecal intussusception and the distal ileum which contained the most concentrated area of polyps was performed.

Enterotomies were then performed at the site of the two ileal intussusceptions. Lipomas measuring approximately 2 by 3 cm. were shelled out from the submucosa.

Postoperatively, the patient did well and was discharged on April 10, 1959. Efforts to obtain barium gastrointestinal x-rays of the two remaining close relatives have been unsuccessful.

Pathology Report.—The specimen consisted of 195 cm. of the terminal ileum and ascending colon containing 107 submucosal sessile and polypoid lipomas of sizes varying from 5 mm. to 5 cm. in diameter (Figs. 3 and 4). They were scattered throughout the gut, some singly and others in clumps. Microscopic examination revealed lobulated collections of mature fatty tissue, mostly submucosal in location.

Comment.—This patient had experienced intermittent intestinal obstruction due to intussusception for several years before the present admission. She also experienced significant lower gastrointestinal bleeding probably due to mucosal ulceration of a lipoma.

It is possible to enucleate many of the larger lipomas through incisions in the bowel such as was done in this patient. It is anticipated that episodes of intussusception or bleeding may recur which may require further operative treatment.

Fig. 1.

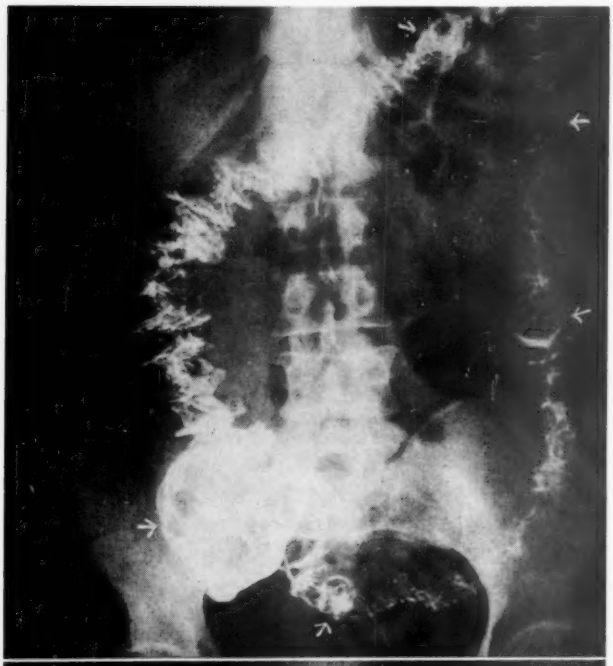

Fig. 2.

Fig. 1.—Postevacuation film from barium enema revealing multiple polypoid lesions in cecum and in colon.

Fig. 2.—Small bowel series demonstrating multiple filling defects from duodenum to ascending colon, ileoileal, and ileocecal intussusception.

Fig. 3.

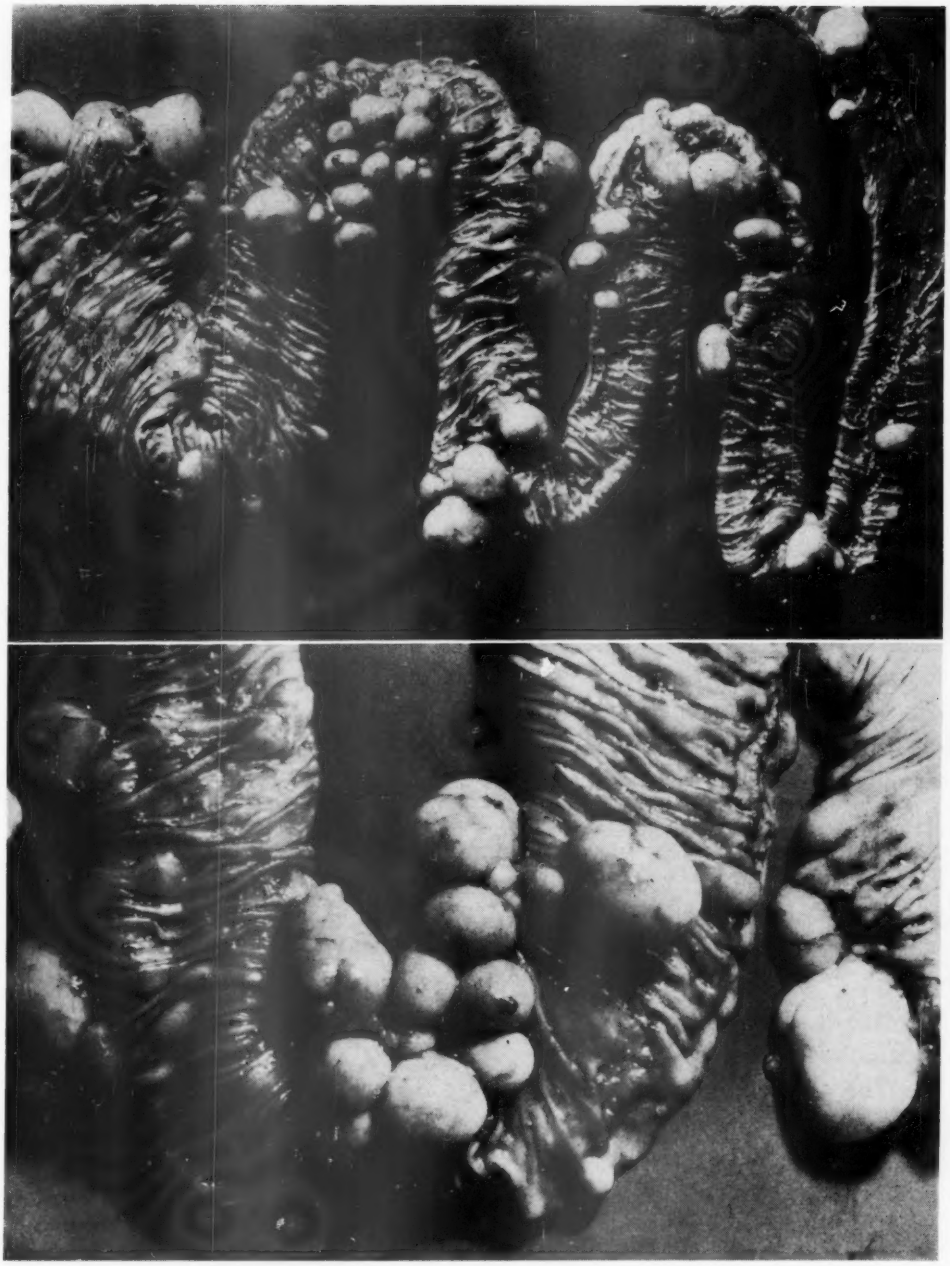

Fig. 4.

Fig. 3.—Segment of resected intestine revealing multiple lipomas.

Fig. 4.—Close-up of resected segment of intestine which contained the heaviest concentration of lipomas.

DISCUSSION

There may be no signs or symptoms of lipomas of the intestines. Many of the reports in the literature represent incidental findings at autopsy. Symptomatic lipomas usually arise in the submucosa and project into the lumen. Symptoms are usually due to intussusception caused by lipoma. Bleeding due to ulceration or trauma to the mucosa overlying a lipoma is less common. Lipomas of the colon which produce symptoms occur twice as frequently as lipomas of the small intestine.

On barium x-ray examination, submucosal lipomas produce a filling defect. A "soap bubble" appearance may be seen when multiple polypoid lesions are present. Lipomas may be more radiolucent than the surrounding tissues and, due to their compressibility, change in shape during the examination when external pressure is applied.

There were several diagnostic possibilities considered preoperatively in this patient. The x-ray pattern was compatible with either familial or multiple polyposis. However, it is unusual for a patient with either diagnosis to survive to the age of 60 years. Most succumb to carcinoma of the colon before 50 years. The Peutz-Jegher's syndrome consisting of intestinal polyposis and mucocutaneous melanin pigmentation could be excluded because of the absence of the pigment spots. In retrospect, therefore, we believe that the diagnosis of intestinal lipomatosis can be correctly made preoperatively.

The operative procedure in such patients is largely designed to relieve obstruction or bleeding and only secondarily to rule out the possibility of malignancy. Care must be taken to conserve as much of the intestine as is possible. If the diagnosis of lipomatosis is confirmed at laparotomy, the larger lipomas may be "shelled-out" through multiple serial enterotomies. A limited resection of the segment of intestine which contains the greatest concentration of lipomas may be indicated.

Prognosis is good, although recurrent intussusception or gastrointestinal bleeding may occur. This entity is probably not familial.

CONCLUSION

1. A patient with diffuse symptomatic submucous lipomas of the intestine is reported.

2. The clinical picture of diffuse intestinal lipomas may be identified preoperatively.

3. Operative treatment should be conservative and should consist of enterotomy and shelling out of the lipoma or limited resection of the intestine in which the greatest concentration of lipomas exists.

4. The prognosis is good, but symptoms of intestinal obstruction or bleeding may recur.

5. A familial incidence has not been established.

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EXPERIMENTAL STUDIES OF HEPARIN-PROTAMINE ACTIVITY WITH SPECIAL REFERENCE TO PROTAMINE INHIBITION OF CLOTTING

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AFTER the neutralization of heparin by protamine, it is commonly observed that the coagulation time of the blood fails to return entirely to normal levels. This phenomenon is frequently assumed to be due to insufficient protamine even though the customary protamine dosage of one to two times the amount of heparin originally given should be not only adequate, but excessive.[3, 4] Protamine itself is known to have a specific anticoagulant action and the hazard of excessive doses has been the subject of occasional speculation as a cause of abnormal clotting after the neutralization of heparin; nevertheless, there is little evidence in the literature on the actual danger of protamine inhibition of clotting based upon quantitative in vivo studies. With the increasingly widespread use of extracorporeal circulation, this problem is now of sufficient practical importance to justify documentation of the precise quantitative and qualitative relations of these drugs.

A series of experiments was carried out in dogs with the objectives of determining whether protamine inhibition of blood coagulation was possible or likely with the amounts of protamine commonly used clinically and defining quantitatively the relationships of these drugs in their effect on blood clotting.

METHODS

Experimental studies were carried out on adult healthy mongrel dogs. The animals were lightly anesthetized with sodium Pentothal and a plastic cannula was introduced through a femoral vein into the vena cava. The cannula was well flushed by withdrawal of blood before samples of blood were taken for testing.

THE EVALUATION OF BLOOD COAGULATION

A protamine† titration test was used to determine the relative heparin-protamine levels, performed as described by Perkins[6] with slight modification In a series of 12 test tubes, 13 by 100 mm., increasing amounts of protamine

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†Protamine Sulfate Injection, N.F., 1 per cent, Eli Lilly & Co., was used in these experiments.

were placed as follows: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, and 1,000 gamma. Appropriate amounts of normal saline were added to each tube to bring the amount of liquid in each to 0.1 ml. When blood was drawn for testing, 1.0 ml. was immediately placed in each tube and the tubes were inverted once for mixing. The tubes were allowed to stand without agitation and were read for clotting at 15, 20, and 25 minutes by tilting to horizontal. Sample titration results are shown in Table I with interpretation. A three-tube Lee-White coagulation time was determined simultaneously with each protamine titration.

TABLE I. SAMPLE TITRATIONS WITH INTERPRETATION

PROTAMINE (γ/ML.)	0	5	10	15	20	25	30	35	40	45	50	1,000
Heparin excess												
After 15′	O	O	O	O	O	X	X	X	X	X	X	O
After 20′	O	O	O	O	X	X	X	X	X	X	X	O
After 25′	O	O	O	O	X	X	X	X	X	X	X	O
Complete neutralization												
After 15′	X	X	X	X	X	X	O	O	O	O	O	O
After 20′	X	X	X	X	X	X	X	X	O	O	O	O
After 25′	X	X	X	X	X	X	X	X	X	X	X	O
Borderline inhibition												
After 15′	X	O	O	O	O	O	O	O	O	O	O	O
After 20′	X	X	O	O	O	O	O	O	O	O	O	O
After 25′	X	X	X	X	X	X	X	X	X	X	X	O
Moderate inhibition—protamine excess												
After 15′	O	O	O	O	O	O	O	O	O	O	O	O
After 20′	X	O	O	O	O	O	O	O	O	O	O	O
After 25′	X	X	X	X	O	O	O	O	O	O	O	O

X indicates clot and O no clot.

EXPERIMENTAL PLAN AND RESULTS

Heparin Inactivation.—Varying doses of heparin* were administered intravenously to 13 animals and serial protamine titrations were performed at hourly intervals, the first titration being carried out 15 minutes after the administration of heparin. The "disappearance" curves of heparin, as illustrated in Fig. 1, were plotted in terms of the protamine equivalent, that is, the amount of protamine required to produce clotting at a normal time in 1 ml. of blood as obtained from the protamine titration. The curves of heparin disappearance with different dosages are similar in slope and the disappearance times were proportional to the initial concentrations of heparin. These disappearance curves are of consequence in considering protamine dosage since the minimal amount of protamine required for neutralization will be affected by the time elapsed following the administration of heparin and the resultant residual heparin level. In general, the level of heparin, as measured by this test, decreased by approximately 50 per cent per hour (mean 57.2 per cent; S.D. 17.8 per cent).

*Heparin sodium, Abbott Laboratories, 1,000 units per c.c. (10 mg.), used in all experiments.

In Vitro Neutralization of Heparin by Protamine.—Fresh samples of blood were drawn into flasks containing known quantities of heparin. Protamine titrations were performed on these samples to determine the relative proportion of protamine necessary to neutralize the heparin and produce normal clotting. In all cases protamine in amounts of 100 to 150 per cent by weight of the administered heparin produced complete neutralization of heparin in vitro.

In Vivo Neutralization of Heparin by Protamine.—

Protamine given at 15-minute intervals: In a series of 26 dogs heparin was given intravenously in dosages of 1.0 to 4.0 mg. per kilogram, the majority of the dogs receiving 2.5 mg. per kilogram. Fifteen minutes later a titration was performed and a predetermined amount of protamine given immediately. At subsequent 15-minute intervals the titration was repeated and additional protamine was given until a total dosage equal to 200 per cent of the original heparin dose by weight was reached. Simultaneous determinations of clotting time by the Lee-White method were performed with each titration.

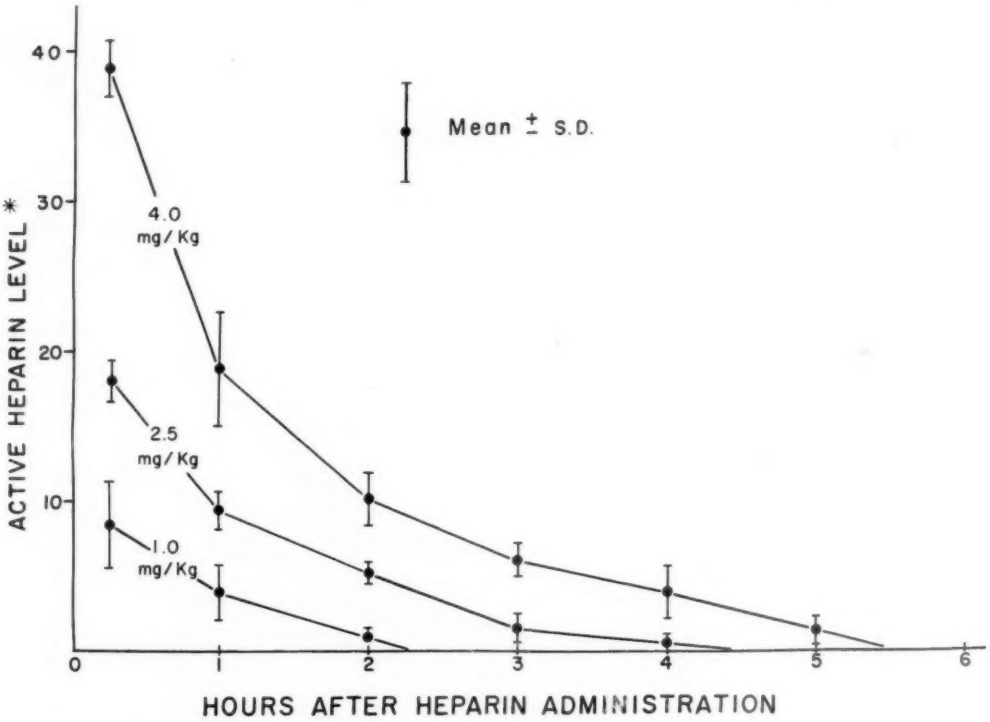

Fig. 1.—Heparin inactivation rate. *The active heparin level is given in gamma of protamine per milliliter required to neutralize the heparin and produce a normal clotting time in vitro.

Table II summarizes qualitatively the results of these studies at each level of protamine dosage.

It was found that doses of protamine of 75 per cent or more by weight of the heparin given invariably produced complete neutralization. With protamine dosages from 100 to 200 per cent of the heparin given, there was an irregular, but marked, incidence of protamine inhibition of clotting; this phenomenon occurred in 14 of the 26 dogs, 11 of 22 tests at the 150 per cent level and 12 of

TABLE II. RELATION OF PROTAMINE DOSE TO BLOOD CLOTTING

EXPERIMENT NUMBER	PROTAMINE DOSAGE IN PER CENT OF ORIGINAL HEPARIN DOSE BY WEIGHT							
	37	50	75	90	100	125	150	200
1	0						+	+
2	−				0			0
3		−			+		+	+
4		−					+	
5		0					0	0
6		−			0		0	
7			0		+		+	+
8			0				0	+
9			0				0	0
10				0			+	+
11				0			+	+
12				0			0	0
13					0		0	0
14					0		+	+
15					0		0	0
16					0		+	0
17					0		+	+
18					0		+	
19					0		0	
20					0		+	+
21						0		+
22						0		0
23						0		0
24							0	+
25							0	+
26							0	0
Totals								
−	1	3						
0	1	1	3	3	10	3	11	10
+					2		11	12

Minus (−) indicates heparin excess.

Zero (0) indicates complete neutralization of heparin with clotting time within 5 minutes of control levels.

Plus (+) indicates protamine excess with prolongation of clotting time of 5 minutes or more above control levels.

22 at the 200 per cent level. There was a significant increase in the incidence of protamine inhibition of clotting at the 150 per cent level as compared to 100 per cent or less ($0.05 > P > 0.02$) but not at the 200 per cent level as compared to 150 per cent ($P > 0.05$).

Table III gives the quantitative degree of prolongation of clotting produced by protamine inhibition in the same experiments. The mean maximum increase in coagulation time of all dogs was 5.8 minutes above control levels; this increase is significant at the 0.1 per cent level ($P < 0.001$).

Protamine given 40 to 70 minutes after heparin: In 18 dogs protamine was administered 40 to 70 minutes after heparin dosages in the same range as above. Similar observations to the first group were made and the results are shown in Table IV. In this group protamine equal to 50 per cent or more of the heparin dose was consistently sufficient to neutralize the residual active heparin. Similarly, protamine inhibition of clotting was seen at lower dosages, occurring in 8 of 15 dogs at the 100 per cent level and in all cases between 150 and 200 per cent. These observations are consistent with the observed inactivation rate of heparin (Part I) which tends to result in increasingly excessive doses of protamine with the passage of time, unless appropriate adjustment in protamine dosage is made.

TABLE III. THE DEGREE OF INCREASE IN CLOTTING TIME WITH PROTAMINE INHIBITION

EXPERIMENT NUMBER	CLOTTING TIME IN MINUTES		
	CONTROL	HIGHEST AFTER PROTAMINE	CHANGE
1	5.0	39.0	+34.0
2	16.0	16.0	0.0
3	12.0	19.5	+7.5
4	6.5	13.0	+6.5
5	6.0	8.5	+2.5
6	15.0	15.0	0.0
7	6.0	22.0	+16.0
8	14.0	20.5	+6.5
9	6.0	5.0	-1.0
10	15.0	33.0	+18.0
11	15.0	21.0	+6.0
12	17.0	16.0	−1.0
13	7.5	6.0	−1.5
14	18.0	26.5	+8.5
15	6.5	6.5	0.0
16	3.0	8.5	+5.5
17	4.5	10.0	+5.5
18	6.0	11.5	+5.5
19	7.0	7.0	0.0
20	3.5	3.5	0.0
21	9.5	24.5	+13.0
22	7.0	7.0	0 0
23	3.5	7.5	+4.0
24	5.0	12.5	+7.5
25	10.0	16.5	+6.5
26	9.0	12.0	+3.0
Mean	9.0	14.9	+5.8
S. D.	4.6	8.8	6.8
S. D. mean	0.92	1.76	1.36

In each instance, the maximal increase is given even though in a few experiments this level occurred at less than the maximal dose of protamine.

TABLE IV. THE RESULTS OF DELAYED ADMINISTRATION OF PROTAMINE (GIVEN 40 TO 70 MINUTES AFTER HEPARIN)

EXPERIMENT NUMBER	PROTAMINE DOSAGE IN PER CENT OF ORIGINAL HEPARIN DOSE					
	20	50	75	100	150	200
1	–			0		
2	0			0		+
3	–			+		
4	0			0		
5		0				
6		0		0		
7		+		+	+	
8			0	+	+	+
9			0			
10			+	+	+	
11			0			
12				0	+	
13				+		
14				+	+	
15				0		
16				0		
17				+		
18				+		
Totals						
–	2					
0	2	2	3	7		
+		1	1	8	5	2

Minus (–) indicates heparin excess.

Zero (0) indicates complete neutralization of heparin with clotting time within 5 minutes of control levels.

Plus (+) indicates protamine excess with prolongation of clotting time of 5 minutes or more above control levels.

The Effect of Additional Protamine Dosage.—There was not a direct relationship between the relative amount of protamine given and the degree of inhibition of clotting. In a number of cases moderate inhibition was evident with relatively small doses and administration of more protamine did not prolong the clotting time further. In a few cases each successive dose of protamine produced successively greater inhibition of blood coagulation, as illustrated in Table V. It is significant that in few cases was the prolongation of clotting time greater than 15 minutes.

TABLE V. EFFECT OF REPEATED DOSES OF PROTAMINE

PROTAMINE (γ/ML.)	0	5	10	15	20	25	30	35	40	45	50	1,000	COAGULATION TIME (MINUTES)
Control													
After 15 minutes	X	O	O	O	O	O	O	O	O	O	O	O	
After 20 minutes	X	X	O	O	O	O	O	O	O	O	O	O	11
After 25 minutes	X	X	X	X	X	X	X	X	X	X	X	O	
After heparin—2.5 mg./Kg.													
After 15 minutes	O	O	O	O	O	O	X	X	X	X	X	O	
After 20 minutes	O	O	O	O	O	O	X	X	X	X	X	O	>60
After 25 minutes	O	O	O	O	O	O	X	X	X	X	X	O	
After protamine—50%													
After 15 minutes	X	X	X		X	X	X	X	X	X	X	O	9
After 20 minutes													
After 25 minutes													
Plus protamine—50%													
After 15 minutes	O	O	O	O	O	O	O	O	O	O	O	O	
After 20 minutes	O	O	O	O	O	O	O	O	O	O	O	O	19
After 25 minutes	X	O	O	O	O	O	O	O	O	O	O	O	
Plus protamine—100%													
After 15 minutes	O	O	O	O	O	O	O	O	O	O	O	O	
After 20 minutes	O	O	O	O	O	O	O	O	O	O	O	O	24
After 25 minutes	O	O	O	O	O	O	O	O	O	O	O	O	
Plus protamine—100%													
After 15 minutes	O	O	O	O	O	O	O	O	O	O	O	O	
After 20 minutes	O	O	O	O	O	O	O	O	O	O	O	O	39
After 25 minutes	O	O	O	O	O	O	O	O	O	O	O	O	

DISCUSSION

Protamine is a strongly basic proteinlike substance which has been known to produce effective neutralization of the anticoagulant effect of heparin since 1937.[2]

Protamine itself acts as an anticoagulant,[1, 4, 7] although not nearly so strong a one as heparin. This effect has been considered to be due to the inactivation of thromboplastin by the formation of a precipitate with the lipoid moiety of thromboplastin.[7] When protamine is given in the presence of heparin, the natural tendency is for them to combine with each other rather than with other blood elements, thereby neutralizing their respective anticoagulant effects. From this it would appear that an excess of either would permit that excess portion

to exert its anticoagulant effect on the blood. Such a reaction has been well demonstrated for heparin and the present studies suggest a similar event may occur with protamine. The majority of previous studies have been performed only in vitro and there has been little quantitative information on the anticoagulant effect of protamine in vivo, particularly as related to its use in neutralization of heparin.

Perkins and associates[5] stated that they had observed abnormal clotting produced by moderate dosages of protamine, but they did not cite quantitative studies. In the present studies protamine was found frequently to produce inhibition of clotting of some degree at levels of administration well within ranges which are frequently used clinically, that is, 100 to 200 per cent of the heparin dose.

When a single neutralizing dose of protamine is given, it is not unusual to find the coagulation time returning almost, but not quite, to normal levels. It has been common practice when this finding is present to give a supplementary dose of protamine, assuming incomplete neutralization of the heparin. It appeared in the present experiments that it was much more common for this abnormal clotting time to be due to protamine inhibition of mild degree than to heparin excess. Furthermore, it was found that when a moderate degree of protamine inhibition has occurred the administration of further doses of protamine in many cases resulted in a progressive prolongation of the clotting time. This secondary prolongation of coagulation time could be interpreted as a "heparin rebound" if simple clotting times were used as an index of heparin neutralization. Such a phenomenon has been used to provide an explanation for a secondary increase in clotting time after heparin neutralization, presumably postulating a release of previously inactivated heparin. No evidence was found suggesting the occurrence of "heparin rebound" but the present studies may provide an alternative explanation for a secondary rise in clotting time.

It should be recognized that the degree of inhibition of clotting produced by protamine in the quantities used (up to 200 per cent of the heparin dose) was not great compared to that produced by heparin. The usual increase was only 5 to 10 minutes above the control time and in only 3 animals was the increase greater than 15 minutes. Presumably, this abnormality could be further exaggerated by additional protamine. The rather wide variation in this reaction is not readily explained, but may be related to a certain quantitative or qualitative biologic variation in the clotting factors normally present in the blood.

Other investigators have also found that, although a dosage of protamine varying from 100 to 150 per cent of the amount of heparin is necessary for neutralization in vitro,[4] an amount equal to 60 to 80 per cent of the heparin dosage produces neutralization in vivo.[3, 4] Despite these findings, it has been common clinical practice to administer protamine in amounts of one to two times the amount of heparin and, if the clotting time does not return entirely to normal, to administer a further dose of protamine. In the present studies the minimal amount of protamine which could be relied upon to neutralize completely the anticoagulant effect of a given amount of heparin was 75 per cent

of the heparin dose by weight. In no case was a larger dose of protamine found to be inadequate. The longer the time interval after administration of heparin, the less protamine is required due to the rapid decrease in effective heparin levels. At the end of one hour a protamine dosage of 50 per cent by weight of the heparin given originally was consistently adequate to provide complete neutralization.

Caution should be used in applying the quantitative results of these studies directly to the post–extracorporeal circulation state. It is our preliminary impression that the amount of protamine required may be slightly increased in this circumstance, but that the danger of protamine inhibition may also be greater. This may be related to some decrease in the level of clotting factors during perfusion. We have been disappointed in the use of the protamine titration alone, as proposed by Perkins and co-workers,[6] as a method of estimating the amount required since in our hands uniform optimum neutralization was not obtained and we tended often to have overadministration of protamine with some degree. It is our present practice after perfusion to administer immediately a dose of protamine equal to 80 per cent of the original heparin dose by weight with some empirical adjustment depending on the duration of time following the administration of heparin. If subsequent protamine titration and clotting time does not indicate complete neutralization, the residual amount of protamine required can be more accurately estimated by the degree of change between the two titrations.

SUMMARY

1. Experimental studies were carried out in dogs to determine the quantitative aspects of protamine inhibition of blood coagulation with particular reference to this occurrence following neutralization of heparin.

2. The rate of disappearance of active heparin from the blood was observed to be approximately 50 per cent per hour in dosages ranging up to 4.0 mg. per kilogram. This is of significance both in calculating duration of heparin activity and in estimating the amount of protamine needed for neutralization.

3. Quantitative studies of the amount of protamine needed for neutralization of heparin indicated that 75 per cent or more of the original heparin dosage by weight consistently provided complete neutralization. With increasing time after heparin administration, progressively less protamine was needed.

4. Quantitative studies indicated that protamine inhibition of clotting may be produced with dosages of protamine within the range commonly used clinically (100 to 200 per cent of the heparin dose). The observed increase in coagulation time above normal was usually small, rarely exceeding 15 minutes.

5. Protamine inhibition of clotting was found frequently to be progressively increased by successive doses, illustrating the danger of additional administration of protamine when the original neutralization of heparin has been erroneously assumed to be incomplete on the basis of a slight abnormality of clotting time.

6. Evidence for a "heparin rebound," in the sense of a secondary or delayed rise in the level of active heparin, was not observed. The possibility of

protamine inhibition of coagulation being incorrectly interpreted as "heparin rebound" was considered.

ADDENDUM

Since submission of this paper, observations have been obtained on the rate of heparin inactivation during prolonged perfusion on a patient. Serial protamine titrations performed during a 4-hour period of total body perfusion in a patient undergoing open heart surgery showed a decrease in active heparin levels which corresponded rather closely with those obtained experimentally. The actual rate of decrease in active heparin levels in the patient during perfusion was approximately 43 per cent per hour.

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EVALUATION OF NEOMYCIN-HYDROCORTISONE OINTMENT IN THE OPEN TREATMENT OF EXPERIMENTAL THERMAL BURNS: DEVELOPMENT OF APPARATUS FOR PRODUCING STANDARD BURNS

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TOPICAL hydrocortisone has proved therapeutically effective in many inflammatory skin diseases. For this reason we began, about 4 years ago, to use this drug on a number of patients with first-, second-, and deep second-degree thermal burns. The rapidity with which healing consistently occurred as well as the lessened discomfort and apparent lessening of scar formation was impressive. The results were even more impressive when a neomycin-hydrocortisone ointment was used.

These clinical observations were not in agreement with the findings of several previous investigators. Kanof,[8] in 1955, produced second-degree thermal burns in human volunteers, and found that hydrocortisone ointment applied topically failed to lessen the intensity or speed the recovery of the burn. In fact he believed that the burns may have been made worse by the treatment. Also in 1955, Wilson, Kimball, and Swenson[12] used topical hydrocortisone alone and hydrocortisone combined with neomycin on partial and full-thickness burns on rats, and concluded that the steroid exerted no beneficial effect but that the antibiotic reduced surface infection if maceration was avoided. Butterfield,[3] in 1957, found topical cortisone acetate of no avail in preventing blister formation in shallow flash burns on human volunteers. However, Fischer,[4] in 1958, reported that healing was speeded, infections were fewer, and discomfort was lessened by inunctions of neomycin-hydrocortisone ointment on first- to third-degree burns in patients.

Because of the discrepancy between results reported by these investigators and the excellent clinical results found by Fischer and in our own experience, we decided to re-investigate this problem on experimental animals under controlled conditions. The first requisite was to produce, if possible, exactly standardized thermal burns. To this end an apparatus meeting our requirements was devised and tested satisfactorily for reproducibility of results. Standardized contact burns were then produced on experimental animals. The burns were divided into treated and control groups, and the progress of the healing process was studied grossly and histologically.

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DEVELOPMENT OF EXPERIMENTAL BURN APPARATUS

Criteria for Establishing Standard Burns.—Before proceeding with this investigation it was necessary to find an accurate yet practical method of reproducing a standard contact burn. The six criteria enumerated by Brooks and associates[2] for the production of the standard burn required in such an investigation seemed most appropriate. To these we would add two further conditions: (1) the burn should be located on such a portion of the animal's body that it will not be unduly traumatized by the animal itself, and (2) exposure time should simulate as closely as possible that of contact burns in humans (a few seconds or less).

A deep second-degree burn was selected as the type to be used in this study because it could be produced easily according to the afore-mentioned criteria, and also complete epithelization could occur with or without treatment.

Types of Burning Apparatus Previously Used.—Review of the literature revealed that many methods and apparatus have been devised and used for the production of controlled thermal trauma. In 1932 Hudack and McMaster[7] devised small glass bulbs with circulating hot water for heating the ears of mice. Leach and associates[9] developed a circular brass heating iron through which heated water circulated at a constant temperature; the applicator surface was constructed of thin, tinned metal for better conduction of heat than the glass bulbs of Hudack and McMaster. Ham[5] used two methods: a flask of boiling water was held against porcine skin or portions of the skin were dipped in an 80° C. waterbath, each for various intervals of time. McCarthy[10] also used scald burns by immersing the backs of white rats in a constant temperature waterbath. Brooks and co-workers,[2] and Moritz and Henriques,[11] as well as Bennett and Dingman,[1] used chambers containing circulating heated water, much the same in principle as the Leach, Peters, and Rossiter apparatus but with refinements to make possible a more standardized burn.

The Moritz and Henriques apparatus consisted of a metal cup applied over a sponge rubber ring, with an adjustable rate of flow of the circulating water. This permitted direct exposure of the surface of the skin to the heated water, thus eliminating an appreciable temperature gradient through a metal surface between the liquid and the skin. There was no insulation of the surface by a static layer of gas, liquid, or solid, nor was heat lost through vaporization of surface moisture. Kanof[8] used the same apparatus for producing burns on human volunteers, except that methyl alcohol was used as the heated liquid which could be maintained easily at 63° C. (its boiling point). Wilson, Kimball, and Swenson[12] used a temperature-controlled hot iron on rats. All these investigations were concerned with the production of contact burns. In the more recent literature interest has centered on atomic flash burns. The flash burn apparatus produced the type of burn used by Butterfield[3] as well as by Henshaw and Pearse[6] in their investigations of the effects of topical medication.

Development of a New Burning Apparatus.—We believed that the most satisfactory apparatus for producing standard contact burns should have certain requisites: (1) It must be capable of reproducing identical burns in different

animals. (2) The burning surface of the applicator must be constructed to maintain a constant temperature so that the heat loss between it and the skin surface is minimal and so that several identical burns can be made during a short period of time. (3) The applicator should be constructed of a lightweight material so that excessive pressure need not be exerted on the skin. (4) The apparatus should be as simple and compact as possible, preferably portable, easily used, and conveniently stored.

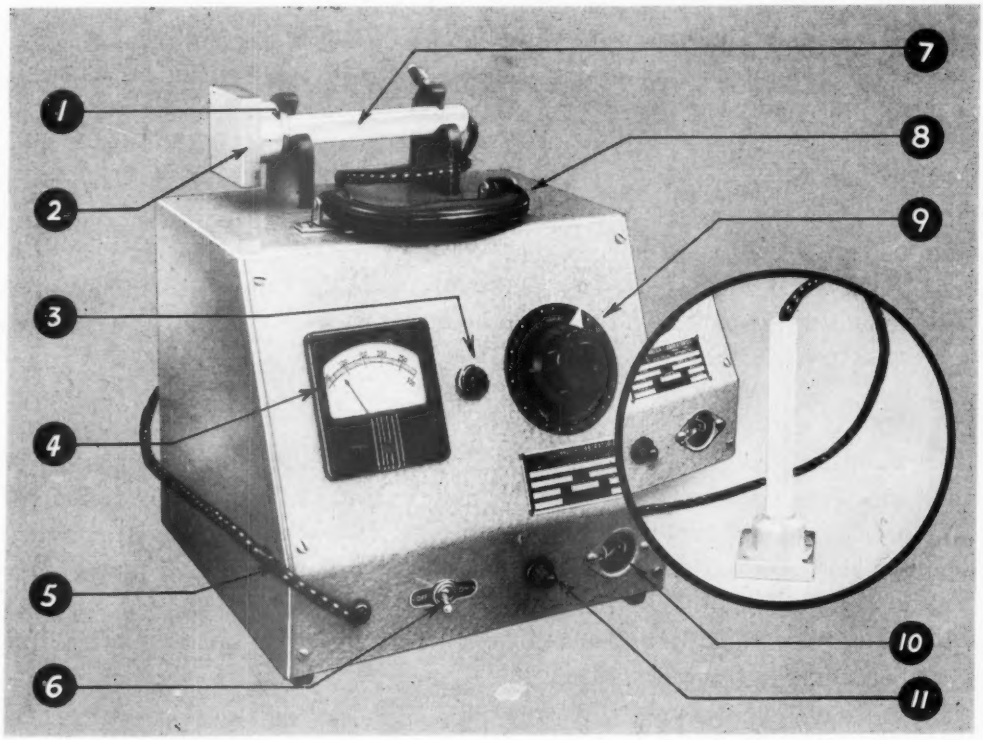


Fig. 1.—The apparatus is compact, portable, and easy to use. *1*, Heat applicator. *2*, Burning surface. *3*, Pilot lamp (indicates power on). *4*, Temperature-indicating meter. *5*, Connection from unit to applicator. *6*, Line switch. *7*, Heat-insulated holder. *8*, Carrying handle. *9*, Temperature selector. *10*, Line input. *11*, Fuse. The inset shows the applicator dismantled and ready for use.

With these requisites in mind, we consulted a manufacturer of electrical equipment (Heidenreich Laboratories of Buffalo, New York) and together we devised a portable unit which provided a source of steady heat that could easily be applied to the experimental animal. The unit was designed to produce temperatures ranging from 0° to 300° F., making it suitable for producing contact burns of any magnitude.

This unit consists of a 115 volt operated, variable voltage source feeding into an isolation transformer which delivers low voltage (30 volts maximum) to the burning applicator. Since the transformer isolates the low voltage to the applicator from the 115 volt line, full protection is provided against voltage in excess of that required. This low voltage protects the operator against electrical hazard when applying the burning device.

The applicator (Fig. 1, *1*) has a corrosion-resistant head containing a specially designed heating element. Measurement of heat at its surface is read from a meter calibrated in degrees Fahrenheit, and accurate reading is obtained by the use of a thermocouple imbedded to within $\frac{1}{32}$ inch beneath the surface of the contact plate. The contact face measures 2 by 2 inches, thus easily permitting connected areas of this size to be burned. Temperature variation of the applicator is obtained by the temperature selector and is thermostatically controlled to prevent heating beyond 300° F. Should a fluctuating line voltage be a problem (which was not the case in our laboratory), a voltage stabilizer could be inserted easily between the line supply and the unit. The applicator is so constructed as to be impervious to moisture; it is easily cleaned and sterilized. Attached to the burning surface of the applicator is a holder made of a low-conduction plastic material (Fig. 1, *7*).

Electrical units are housed within a neatly finished metal case which is fitted with a support for the applicator and a handle for lifting and carrying the unit (Fig. 1). It may be plugged into any convenient 115 volt, 60 cycle outlet. A signal light indicates when the applicator is being heated. The convenient grouping of controls, which indicate power switch and protector fuse, may be seen in the illustration.

MATERIAL AND METHOD

Preparation and Production of Burns.—Healthy adult buck rabbits weighing 4.5 Kg. were selected for the study, mainly because they could be handled easily and maintained under control conditions. Each animal was anesthetized with intraperitoneal sodium pentobarbital, 1 c.c. for every 2 Kg. of body weight. The skin of the paraspinous area of the back was shaved on one side with care not to abrade the skin. The shaved area was thoroughly cleansed with ether and alcohol and was allowed to dry.

Preliminary experiments with time and temperature, using several rabbits, followed by gross and histologic study of the burn, showed that contact with the applicator for 3 seconds at 250° F. consistently and rapidly produced a deep second-degree thermal burn. This type of burn was produced on the prepared shaved area of each rabbit, using only the pressure of the lightweight applicator itself. The burn area, estimated as a 10 per cent body burn (Fig. 2), measured 2 by 4 inches and was made by two contiguous applications. A period of one hour was allowed to pass before application of any ointment.

In order to eliminate to some degree the factor of individual skin variation, each rabbit was used both as a treated and a control animal. Burn areas were made on opposite sides of the back, allowing an 8-week interval between these experiments.

Treatment.—In order to evaluate the therapeutic effectiveness of the neomycin-hydrocortisone inunction, its constituents were studied separately as a control series. The ointment itself (NHB) was therefore employed in the "treated" series, and the control series was divided into three groups: (1)

those treated with neomycin plus ointment base (NB); (2) those treated with hydrocortisone plus ointment base (HB); and (3) those treated with ointment base (B) alone. The base was a bland water-soluble vehicle; its exact composition was not known. These various medications* were applied one hour following the contact burn and then daily for 3 weeks. All of the burns were treated by the open method. Color photographs were taken at one hour, 24 hours, 7 days, and 21 days postburn.

There were 25 total burns in the series, treated as shown in Table I.

TABLE I

NUMBER OF BURNS	MEDICATION
8	Neomycin + hydrocortisone + ointment base (NHB)
4	Hydrocortisone + ointment base (HB)
10	Neomycin + ointment base (NB)
3	Ointment base alone (B)

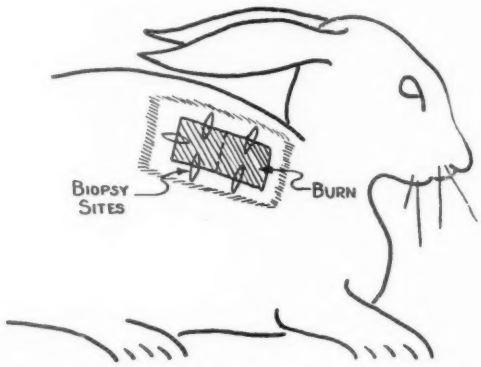


Fig. 2.—The center dividing line illustrates how the burn was produced by using a 2 by 2 inch application on each of two contiguous sites. Location of the specimen for biopsy is also shown.

Microscopic Examination.—Biopsies were taken after 24 hours, 7 days, and 21 days. Elliptical sections were excised so that the juncture of burned tissue with normal skin would appear in the center of the specimen to facilitate microscopic comparison of longitudinal sections of tissue (Fig. 2). All the biopsies were performed with the aid of a general anesthetic (intraperitoneal sodium pentobarbital) in order to prevent interference with the healing process. This was not without some hazard since three of the original 16 rabbits died under anesthesia, reducing the number of burns in the study to 25.

The tissue sections of both treated and control specimens were presented to the pathologist as unknowns for histologic examination on the basis of (1) inflammation, (2) amount of eschar formed, and (3) degree of re-epithelization.

RESULTS

As had been noted by Wilson and associates[13] in their studies of severe burns on rabbits, no blistering occurred because of the lack of sweat glands in

*Supplied by The Upjohn Company in the form of Neo-Cortef, 1 per cent (NHB); Cortef, 1 per cent (HB); Myciguent (NB); and ointment base (B).

the skin of fur-bearing animals. Instead, the 24-hour biopsies of both treated and control groups in this series showed a large amount of edema and inflammation in the subcutaneous tissues.

At the end of 7 days, there was microscopic evidence of inflammation, eschar, and slight re-epithelization in all tissue sections.* At this time the burns to which steroids had been applied (NHB and HB) showed less inflammation grossly than those treated with nonsteroid ointment (NB and B).

At the conclusion of 21 days postburn, as shown in Table II, complete re-epithelization had occurred in all but three of the steroid-treated burns (NHB and HB) and in these three it was almost complete. In all re-epithelized burns in these two groups, no inflammation and minimal or no eschar was noted (Fig. 3, *C* and *D*). Slight eschar was present in 3 of the 4 HB-treated burns and in 1 of 8 NHB-treated burns. In the 3 incompletely re-epithelized burns inflammation was essentially absent.

TABLE II. COMPARISON OF HEALING IN 25 DEEP SECOND-DEGREE BURNS IN RABBITS AT THE END OF THREE WEEKS

	INUNCTION AND NUMBER OF BURNS			
	CONTROL SERIES			TREATED SERIES
RESULTS AT 21 DAYS	OINTMENT BASE (B) (3)	NEOMYCIN + BASE (NB) (10)	HYDROCORTISONE + BASE (HB) (4)	NEOMYCIN + HYDROCORTISONE + BASE (NHB) (8)
Inflammation	Present (3)	Present (9)	Absent (4)	Absent (8)
Eschar	Marked (3)	Marked (10)	Minimal (3) Absent (1)	Absent (7) Minimal (1)
Re-epithelization	Absent (3)	Incomplete (8) Absent (2)	Complete (3) Almost complete (1)	Complete (6) Almost complete (2)

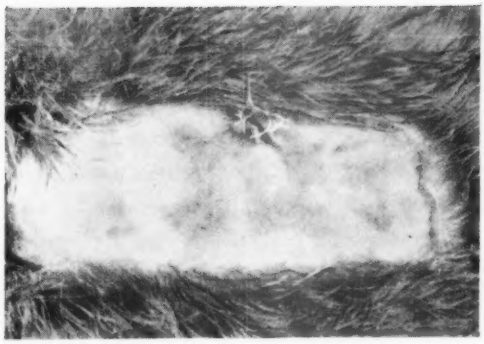
Inflammation was graded upon presence or absence of polymorphonuclear leukocytes in the burned tissue. Eschar was classified according to the amount present both grossly and histologically. Re-epithelization was determined by the degree of histologic regrowth of epithelium in the tissue sections. Numbers in parentheses indicate the total number of burns in each category.

Of the nonsteroid group (NB and B) none of the burns treated with the ointment base alone revealed any tendency toward re-forming epithelium (Fig. 3, *F*). Two of the NB-treated group also revealed no re-epithelization (Fig. 3, *H*), 6 showed very early regrowth, 2 moderate regrowth, but none

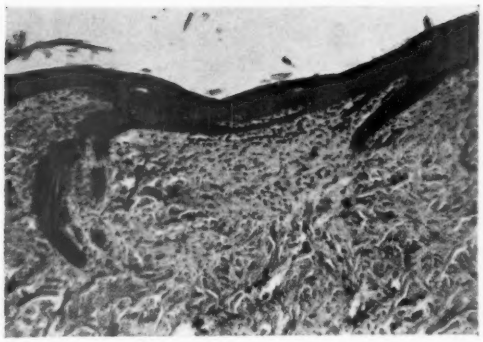
*Biopsies were also performed on 4 rabbits at the end of 2 weeks. Although this was not routine for the series as a whole, it was interesting that the two treated with neomycin-hydrocortisone ointment showed almost complete re-epithelization with no inflammation or eschar at this time (Fig. 3, *A* and *B*) while one treated with base alone and one with neomycin plus base revealed much inflammation and eschar with no epithelium re-forming at this stage.

Fig. 3.—*A*, Gross appearance of an NHB-treated burn at the end of 2 weeks. Re-epithelization is almost complete and there is no eschar. The biopsy site may be seen in the upper mid-portion of the burn. *B*, Biopsy of burn shown in *A* reveals complete re-epithelization, no inflammation, and no eschar. *C*, Gross appearance of an NHB-treated burn at the end of 3 weeks. The burn shows complete re-epithelization and no eschar formation. Three biopsy sites may be seen. *D*, Biopsy of burn shown in *C* after 3 weeks. Re-epithelization is complete and there is no inflammation or eschar.

E, Marked eschar was present in all nonsteroid-treated burns as may be seen in this gross section of the burn shown in *F*. *F*, Microscopic section of a burn treated with base alone. No tendency toward re-epithelization is noted after 3 weeks. Also marked eschar and inflammation are present. *G*, Gross appearance of a burn treated with NB. While moderate eschar is present, definite areas of re-epithelization can be seen adjacent to the eschar. *H*, Microscopic section of a burn treated with NB is almost indistinguishable from that shown in *F*. There is no re-epithelization, and inflammation and eschar are marked.



A.



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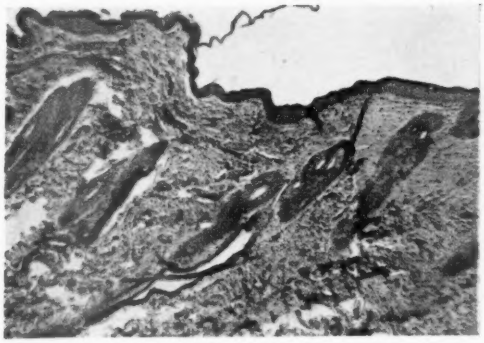

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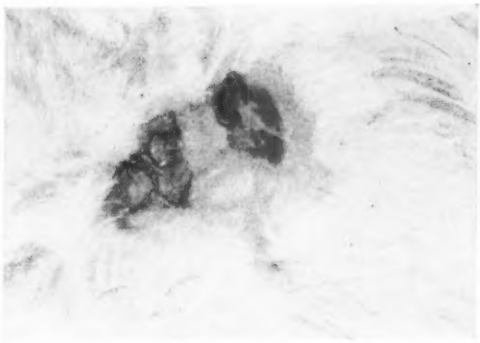
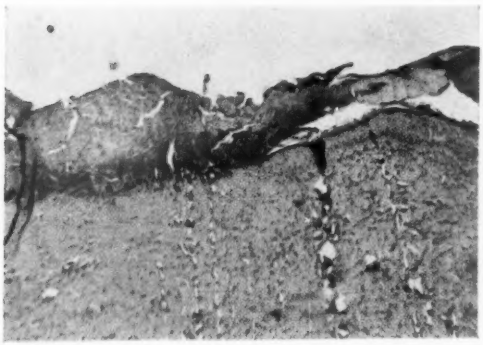


E.

F.

G.



H.

(For legend, see opposite page.)

complete regrowth. A strong inflammatory reaction was still present in all B-treated burns and in all but one of the NB-treated group. There was marked eschar in all nonsteroid-treated burns (Fig. 3, *E*).

In general, healing was most complete in groups NHB and HB (steroid-treated), whereas it was negligible in those treated with ointment base alone (essentially untreated). It was most complete in the NHB group, but the series was too small for this to be significant. The NB group, occupying an intermediate position, more closely resembled in inflammation and eschar the B group; in re-epithelization it tended toward the steroid-treated groups (Fig. 3, *G*).

COMMENT

From this relatively small series it would appear that the ointment containing both neomycin and hydrocortisone promotes more rapid healing, with faster regrowth of epithelium and less eschar formation. The results in the HB group (hydrocortisone plus ointment base), however, were almost comparable. It is significant that the burns treated with neomycin plus ointment base were little better than those treated with ointment base alone. This suggests that the steroid was the key factor involved in healing, but that the antibiotic may be of benefit in preventing surface infection of the healing burn, as was found by Wilson and associates.[12]

It is difficult to discount entirely the unfavorable results found by Kanof[8] in his trials of hydrocortisone treatment of burns in human volunteers. His ointment applications were made at intervals up to 24 hours postburn but not beyond that time, while our inunctions were repeated daily for a period of 3 weeks. We believe that his treatment may have been too brief to be effective upon either human beings or experimental animals. This is borne out by the 136 human burn cases reported by Fischer[4] in which daily applications of NHB were employed. He found that healing was more rapid in these cases and that the patient enjoyed an earlier return to his normal routine.

It is even more difficult to discredit the findings of Wilson and his associates[12] who used on 50 rats the identical commercial ointment (NHB) employed in the present study. The same 3-week period was utilized, but applications were made twice daily, and biopsies were taken at various time intervals. They stated that the burns were made by a temperature-controlled hot iron, but this apparatus and the manner in which it produced a standard burn were not described. They found no essential difference in healing between the treated and untreated animals.

These investigators also used the same ointment on partial and full-thickness burns in human beings for 21 days, making applications two to four times daily on one extremity. The other extremity remained untreated as a control. Again no essential differences in healing were found. Why their results should differ so greatly from those observed clinically by Fischer[4] and both clinically and experimentally by us is difficult to understand. In the different experimental animals used (rats and rabbits), some variation in tissue reaction to medication and to rate of healing may be present, but such gross differences in human burns are puzzling.

It would seem that the problem might be resolved by further, more extensive investigation, under specifically controlled conditions obviating various questionable factors in the afore-mentioned studies. For example:

1. Our purpose in this study was to evaluate the steroid and antibiotic components of the neomycin-hydrocortisone preparation on the rate of burn healing as compared with the ointment base alone, which was considered similar to a bland substance such as petrolatum. Rabbits, therefore, were deemed adequate for the purpose. However, since porcine skin most closely resembles that of the human in its structure and function,[11] pigs would probably yield more comparable data (such as blister formation) than the fur-bearing animals.

2. Skin cultures and sensitivity tests on the experimental animals would determine the specific role of the antibiotic in the healing process. A number of investigators who used an ointment incorporating neomycin ignored this factor, although several stated that the presence of infection could be significant.

3. The series should include a sufficient number of experimental animals. Both of our series and several others reviewed were too small to draw detailed conclusions.

4. It is imperative that experimental burns under study should be identical, without variation in degree, depth, or intensity, although skin variation in animals of the same species may be a somewhat limiting factor. We believe that our apparatus will produce identical standard contact burns, also that by using the same animals in both treated and control groups the factor of skin variation was probably lessened, or even obviated.

5. Daily applications of the therapeutic ointment should be made over a period of time adequate to obtain maximum therapeutic effect (at least 3 weeks in the case of deep second-degree burns).

6. Finally, the burned area should be carefully observed, both grossly and microscopically, at frequent intervals and over a period long enough (3 weeks) for the total effect of the medication upon healing to be evaluated fully. This should be done on both the treated and control groups.

SUMMARY AND CONCLUSIONS

In order to evaluate our favorable clinical impression of a neomycin-hydrocortisone ointment in the open treatment of thermal contact burns, an investigation was undertaken on standard second-degree burns in rabbits. An apparatus was devised which would produce identical standard burns. Various combinations of neomycin, hydrocortisone, and ointment base, as well as base alone, were then applied daily to 25 standard burns over a 3-week period. Biopsy was performed at the end of 24 hours, 7 days, and 21 days.

The results showed that the inunctions incorporating hydrocortisone were superior to those containing no steroid. They resulted in less inflammation, produced less eschar, and promoted more rapid re-epithelization in the healing process of deep second-degree thermal burns.

Although our series is not large, the favorable results obtained experimentally with this medication correlate well with our clinical impression of its value in the treatment of patients over the past 4 years. The neomycin-hydrocortisone ointment demonstrated more rapid healing, less scar formation, and earlier return of function to the injured part than when bland or antibiotic ointments alone were used. Less discomfort was also noted clinically but this factor is impossible to evaluate in experimental animals. The neomycin-hydrocortisone combination was slightly superior to the hydrocortisone ointment; however, the series was too small to draw a definite conclusion on this point. Presumably neomycin has an effect in preventing surface infection.

Since there is still much controversy concerning the effectiveness of the topical use of neomycin-hydrocortisone ointment in the treatment of burns, further experimental study under precisely controlled conditions is necessary before a final conclusion can be made.

Grateful acknowledgment is made to Miss Marjorie E. Jacobson for technical assistance and photographic studies.

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A NEW TECHNIQUE FOR CARDIAC VALVE CONSTRUCTION FROM AUTOLOGOUS DIAPHRAGM

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EXCISION and replacement of a diseased structure is the fundamental aim of any surgical therapy. No such solution in treatment of stenotic, hypoplastic, aplastic, and regurgitant cardiac valves is on hand despite the reality of techniques making excision, plastic procedures, and prosthetic replacement possible.[4, 14]

Prosthetic appliances have been implanted in the area of the diseased valve or peripherally to the lesion. Hufnagel's[6, 7] ball valve has found some degree of clinical acceptance in treatment of aortic regurgitation even though insertion in the descending aorta results only in slight improvement in the percentage of regurgitation while blood flow to the brain and possibly the coronary arteries is reduced.[13]

Another approach is circumferential suture constriction of the valvular ring which may be dilated in patients with regurgitant disease of the aorta.[3, 16] The relief of the physiologic abnormality by raising the diastolic pressure and restoration of a normal aortic pressure will commonly be thwarted when the circumferential sutures become displaced as commonly occurs.

Plastic procedures on the valves such as bicuspid conversion utilize diseased tissues which have lost flexibility and mobility.[1, 12] Some valves will show pronounced degenerative changes as may be observed in fresh autopsy specimens and reconstruction by such means will be futile. These plastic procedures are not applicable in patients with marked congenital pulmonary stenosis or atresia. Sewing of a patch of Ivalon into the pulmonary outflow tract may cause pulmonary regurgitation and may prove to be a temporary measure.[2] The capacity of the outflow tract remains stationary while with growth the demand increases. Direct pulmonary artery anastomosis to the infundibular portion of the ventricle[11] foregoes the advantages of a competent pulmonary valve.

Autologous grafts of veins, homologous aorta with leaflets, and foreign materials were tested as total or partial substitutes in cases of valvular insufficiency with no or only moderate success.[8, 10, 15] Pedicled pericardium seemed to be more satisfactory than many other materials.[5]

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Thrombosis, contraction of grafted materials due to excessive fibrosis, and incomplete restoration of function are some of the problems encountered in attempts to restore a functional cardiac valve. Total excision and replacement of the diseased structure will be the ideal approach to valvular incompetency or stenosis when an adequate prosthetic replacement becomes available.

The search for an acceptable material to supplant or reconstruct a cardiac valve or an appliance replacing such valves continues. An ideal valve should consist of a living tissue with a regenerative and growth potential. It should be simple in construction and mechanically efficient, adding no resistance to outflow while preventing regurgitation.

Autologous diaphragm presents features which seem to fulfill the criteria of a material suitable for cardiac valve replacement. Autologous tissues without argument are from the biologic standpoint ideally suited to any kind of surgical repair, replacement, and reconstruction. The diaphragm is handily available in large enough sheets. Its anatomic peculiarity, namely, composition of the thicker muscular and thin tendinous portion, is eye-catching. The thickness of the pars muscularis corresponds in general to that of the aorta. The tendinous portion quite agreeably duplicates architecturally the semicircular valves of the great arteries and the mitral or tricuspid valves (Fig. 1, *b*). The growth regenerative potential of the diaphragm transplanted in the form of a vascular graft or leaflet is a possibility.

Even though shreds of muscle are a convenient clot-promoting material, liquefaction of clotted blood occurs readily in the serous cavities over the diaphragm.

MATERIALS AND METHODS

The valves were constructed either from the tendinous portion only or from the tendinous and muscular portions of the diaphragm. In the latter case a quadrangular piece measuring approximately 8 by 5 cm. in diameter was excised from the right or the left hemidiaphragm (Fig. 1, *a*) and placed into saline after thorough irrigation with heparin. No difficulty was encountered in the primary closure of the rather large diaphragmatic defects. The margins of the graft were trimmed and special attention was given not to traumatize the graft by handling. The tendinous portion, slightly longer than the breadth of the prospective vessel, was cut at an angle at its lateral margins and inverted to form a cuff (Fig. 1, *c* and *d*). Two 5-0 silk sutures were placed at both extremities and the graft was fashioned with a continuous 5-0 silk suture into a tubular structure which included the inverted tendinous portion at the proximal margin (Fig. 1, *b*, *c*, and *d*). A unicuspid valve is thus formed. Regurgitation is prevented by collapse of the tendinous leaflet toward the suture seam (Fig. 1, *e* and *f*). To prevent regurgitation the leaflet must be slightly longer than its breadth. Diaphragmatic valve vascular grafts thus constructed were interposed by end-to-end anastomosis into the abdominal or thoracic aorta and the first portion of the pulmonary artery.

An alternative procedure was developed applying the tendinous portion of the diaphragm by itself (Fig. 2, *a*). The test artery was transected obliquely and a longitudinal arteriotomy was performed in the anterior aspect of the distal segment (Fig. 2, *b*). A quadrangular tendinous graft was then inserted into the distal portion of the artery and sutured circumferentially to the transected distal arterial end with a continuous 5-0 silk suture. The free margin was inserted into the longitudinal arteriotomy which was closed with a continuous 5-0 silk suture. An end-to-end arterial anastomosis completed the procedure. A similar procedure successfully tried resembles the previous but differs in that the circumferential suture is performed simultaneously with an end-to-end anastomosis interposing the tendinous leaflet in the anastomotic line (Fig. 4, *d* and *e*). In the two last-described procedures oblique transection of the distal arterial segment and proximal arterioplasty is necessary (Fig. 2, *b*).

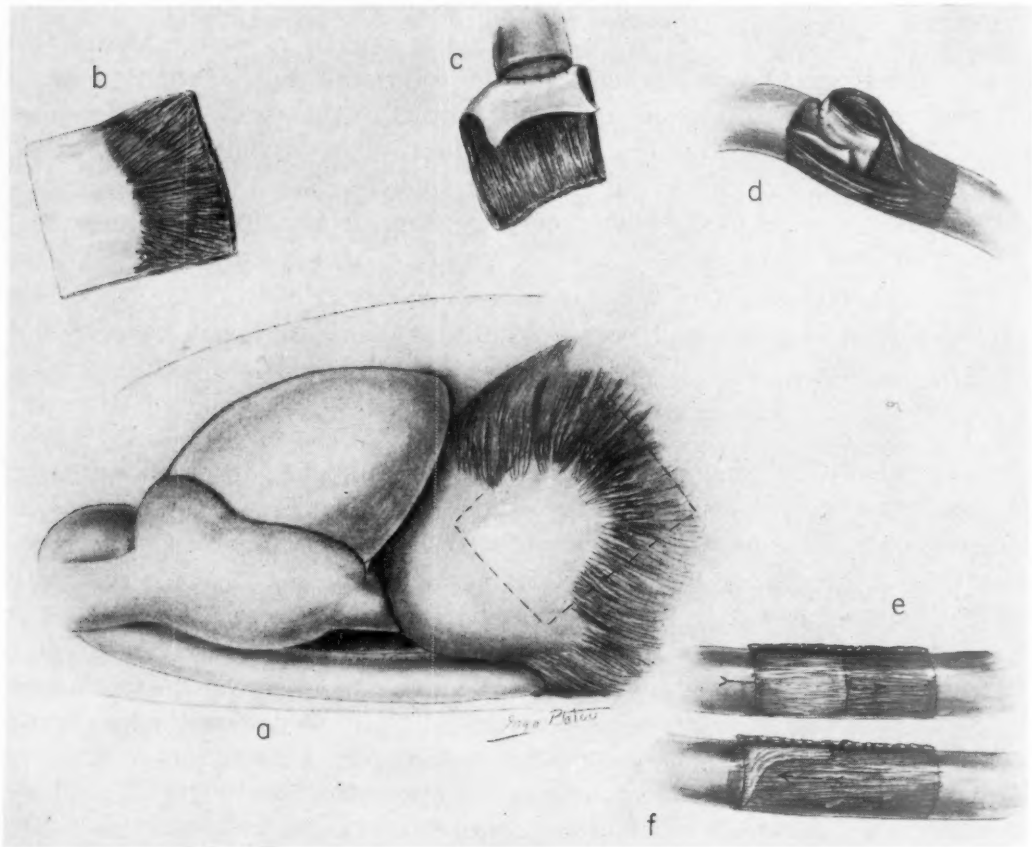

Fig. 1.—Construction of valve graft from tendinous and muscular portion of diaphragm. *a* and *b*, Muscular and tendinous diaphragmatic tissue. *c* and *d*, Construction of tubular valve graft with tendinous cuff inverted. *e* and *f*, Mechanism of function.

During construction of such a valve, narrowing of the arterial lumen will ensue. However, the transverse diameter will be enlarged at the anastomotic line. Special attention must be paid to the free end of the valve leaflet; misplacement of the sutures of the longitudinal closure with inclusion of excess valve material will cause narrowing at the outflow os.

The test sites selected for insertion of the grafts were the abdominal aorta beyond the renal arteries and the arch of the aorta immediately beyond the left subclavian artery using this vessel as proximal limb of a bypass shunt into the descending portion of the thoracic aorta. The pulmonary valve was replaced after excising the leaflets. The graft was attached to the pulmonary orifice and the pulmonary artery with a continuous 4-0 silk suture. A bubble-type oxygenator was utilized to bypass the right side of the heart.

RESULTS AND DISCUSSION

The character of the muscular and tendinous portions of the diaphragm makes this tissue easier to handle than synthetic materials such as Teflon and the tissue is resilient enough to prevent "cutting out" of silk sutures inserted.

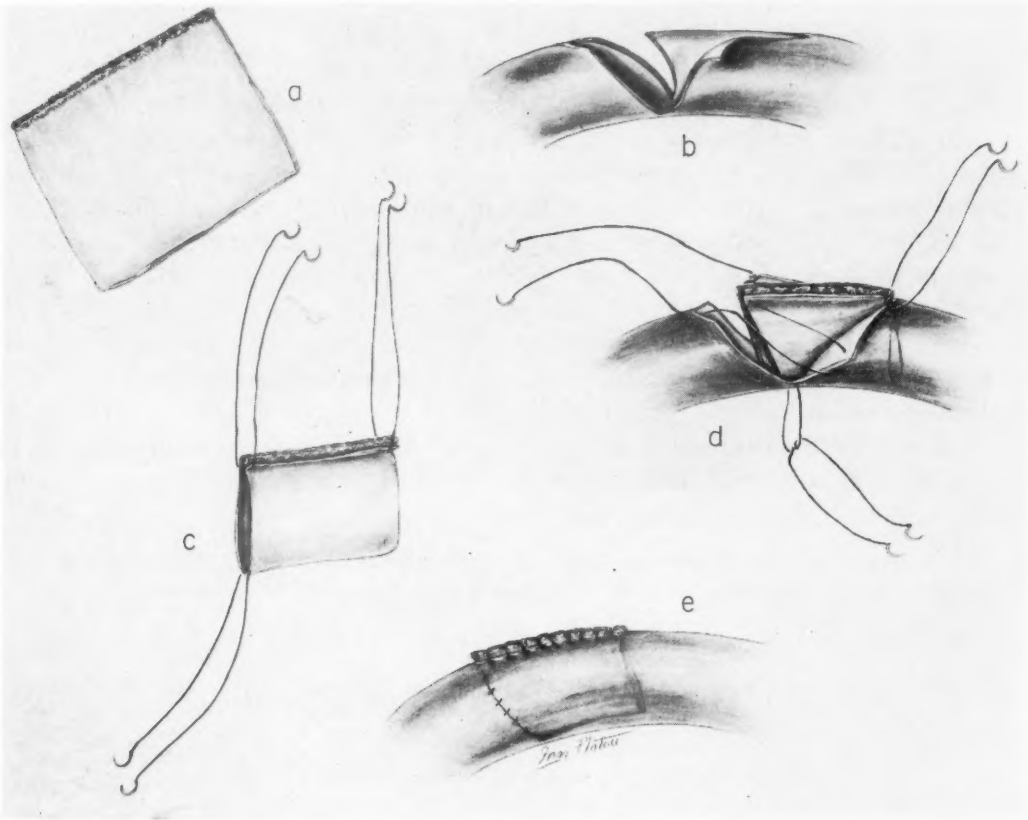

Fig. 2.—Construction of valve from tendinous portion of diaphragm. *a*, Tendinous piece of diaphragmatic tissue. *b*, Transverse and longitudinal arteriotomy. *c*, Tendinous leaflet ready for insertion into the arterial lumen. *d*, Method of suturing leaflet. *e*, Valve in place.

The competence of the valvular grafts in the aorta and the pulmonary artery was demonstrated in vivo by back flow distention of the valve while the vessel being occluded proximal to the graft remains collapsed. An in vivo and in vitro retrograde distention of the valve graft inserted in the aorta and pulmonary artery withstood pressures of 350 to 400 mm. Hg with no evidence of incompetency.

Since upon transection of the aorta or pulmonary artery retraction of the vessel ensues, reconstruction by anastomosis of a tubular prosthetic device into the defect created by transection of the vessel was technically simpler than insertion of a valve into a partially or completely transected vessel. The clinical necessity of replacing a stenotic or athretic pulmonary vessel was another reason for developing the first method.

The possibility of increasing peripheral vascular flow by inserting a valvular graft into the terminal aorta[9] makes construction of a valvular mechanism adaptable to smaller vessels an attractive consideration. Unicuspid sleeve valves as described were found functionally effective in vitro, in acute and short-term experiments upon insertion into the pulmonary artery, and in the thoracic or abdominal aorta of dogs. It was found feasible to insert and suture valves as described into the mitral, tricuspid, and aortic orifices after excision of the respective structures in cadaver hearts.

SUMMARY

A technique of autologous cardiovascular valve construction using the dog's own diaphragm was described. This valve consists of a muscular tube with an inverted tendinous sleeve at the proximal extremity, the competency depending on its collapsing toward the suture line of the longitudinal seam forming the tubular graft. An alternative method was developed, namely, insertion of a rectangular sheet of the tendinous portion of the diaphragm into the transversely transected arterial trunk. An end-to-end anastomosis is performed and the longitudinal margin is fastened to a similarly placed arteriotomy. Such grafts have been inserted into the abdominal aorta, the thoracic aorta, and the pulmonary artery as replacement of the pulmonary valves of dogs. Competency of such valves was demonstrated by retrograde distention to 400 mm. Hg pressure. The feasibility of inserting similar grafts into the mitral, tricuspid, and aortic orifices of cadaver hearts is mentioned.

We wish to express our appreciation to Sister Victorine Long, M.S., Mr. Edward Berger, B.A., Mr. Charles Anderson, and Miss Sally Macho, B.S., for technical assistance.

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SEGMENTAL RENAL ISCHEMIC ATROPHY

Experimental Study of Pathophysiology, Morphology, and Reversibility

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WITH increased use of renal angiography, partial or total occlusion of major renal arterial branches with segmental renal atrophy has become a recognized cause of arterial hypertension in man. Such hypertension has been relieved by uninephrectomy, partial nephrectomy, or excision of atrophic segments.[4, 11] These operations sacrifice all or part of the kidney; they contrast in this respect with conservative measures, such as endarterectomy, segmental arterial excision with anastomosis, arterial grafts, and bypasses, which have relieved hypertension in patients with occlusive lesions of *main* renal arteries. Improved surgical techniques may eventually enable application of reconstructive procedures to lesions of arterial branches; these would be particularly useful in patients whose contralateral renal function is impaired or absent. However, such procedures have not yet been shown to be followed by recovery of function and structure, and relief of hypertension due to arterial branch lesions.

The purpose of this report is to describe observations of renal function and morphology in dogs during and after constriction of major arterial branches. This evaluation indicates that conservative repair of lesions of major arterial branches may be clinically ineffective. The data also clarify aspects of the abnormal physiology and diagnosis of such lesions and bear on the problem of renal hypertrophy.

MATERIALS AND METHODS

The studies were carried out in 4 mongrel dogs weighing from 13 to 20 Kg. Pentobarbital sodium, 25 mg. per kilogram of body weight, was given intravenously during operations and tests done at intervals after uninephrectomy and subcutaneous explantation of the contralateral kidney. Studies of the renal arterial circulation in the dog[10] had established the extent of renal atrophy that would predictably result from occlusion of selected arterial branches. Accordingly, four secondary branches of the upper pole were partially occluded by silver wire clips molded around 23-gauge needles, the aim being to establish polar ischemia and atrophy involving one-fourth of the renal mass. The operations were done at 3, 4, 8, and 10 weeks after uninephrectomy, respectively.

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The clips were allowed to remain in place for an average of 46 (range 42 to 50) days, and biopsy specimens were obtained from the ischemic areas immediately after their removal. The observations were continued over a further period of 56 days, after which the animals were sacrificed and tissues were taken for histologic studies.

Renal function tests were done by methods previously described.[14] These included determinations of plasma clearances of p-aminohippurate (C_{PAH}, ml./min.) at low plasma concentrations, and of mannitol (C_M, ml./min.), taken respectively as equivalent to effective renal plasma flow (ERPF) and glomerular filtration rate (GFR). Mannitol was infused at rates sufficient to maintain osmotic diuresis and plasma concentrations of 30 to 40 mosm. per L. Other functions measured were urinary flow (V, ml./min.); urinary osmolality (U_{Osm}, mosm./L.); osmolar clearance (C_{Osm}, ml./min.); maximum reabsorption of solute-free water, both absolute ($T^c_{H_2O}$, ml./min.), and relative to filtration rate ($T^c_{H_2O}/GFR$); urinary sodium concentration (U_{Na}, mEq./L.); and sodium output ($U_{Na}V$, mEq./min.). From these data, filtration fraction (FF), filtered sodium load (L_{Na}), and the excreted fraction of sodium (EF_{Na}) were calculated. Plasma extraction ratios of PAH (E_{PAH}) were measured during some of the tests; total renal plasma flows were calculated from these and corresponding C_{PAH}, and total renal vascular resistance (R) was calculated as P/TRPF. Femoral mean arterial pressures (MAP) were measured with a mercury manometer during each function test. These tests were done 2 weeks and 1 week before application of the clips; 2, 3, 4, and 5 weeks after application; and 1, 2, 3, 4½, and 9 weeks after their removal.

RESULTS

Hypertension.—Arterial pressure (Fig. 1, Table I) increased 2 weeks after application of the arterial clips and rose thereafter to hypertensive levels. Hypertension remitted only transiently and partially after removal of the clips and increased above previous levels at the time of the last observation.

Morphology.—

Biopsies: Specimens were obtained immediately after removal of the arterial clips. At this time, inspection and palpation of the mobilized portion of the kidney revealed marked polar atrophy in 3 dogs and slight atrophy in one. Lines of demarcation were present at the junctions of atrophic and normal renal segments. Arterial bleeding occurred during incision of the atrophic renal cortex. Microscopically, one specimen showed moderate diffuse congestion of glomeruli and intertubular capillaries; two showed capsular edema and subcapsular focal ischemic atrophy; and the fourth showed intense tubular atrophy, periglomerular fibrosis, and subcapsular round-cell infiltration, the latter extending into intertubular connective tissue.

Necropsies: Three kidneys showed marked polar atrophy (Fig. 2). Lines of demarcation between the atrophic and untouched hypertrophic renal segments extended through the entire upper poles. On section, the atrophic cortices measured 2, 4, and 6 mm. in width, respectively, as compared with those

TABLE 1. REPRESENTATIVE EXPERIMENT (DOG 321) SHOWING RENAL FUNCTIONS BEFORE AND AFTER PARTIAL ARTERIAL CONSTRICTION

DAYS	−20	−8	CLIPS ON 0	+14	+21	+29	+38	CLIPS OFF +46	+56	+64	+76	+82	+118
ERPF (C_{PAH}) ml./min.	128.5	130.8		73.4	69.8	66.5	95.6		115.2	115.7	127.0	108.5	86.4
GFR (C_M) ml./min.	25.6	32.2		19.7	19.7	21.7	24.1		30.3	29.4	30.4	26.2	23.7
E_{PAH}	-	86.0		-	40.5	-	60.7		66.1	-	-	71.6	80
TRPF $\frac{C_{PAH}}{E_{PAH}}$ ml./min.	-	152.1		-	172.3	-	157.5		174.3	-	-	151.5	108.0
FF	0.20	0.18		0.26	0.28	0.32	0.25		0.26	0.25	0.27	0.24	0.27
R $\frac{MAP-10}{TRPF}$	-	0.71		-	0.93	-	1.08		0.92	-	-	1.06	1.63
MAP mm. Hg.	120	118		126	170	185	180		171	163	162	176	186
V ml./min.	2.5	2.6		5.3	5.7	5.0	4.8		6.3	5.9	6.2	3.7	5.6
$T^c_{H_2O}$ ml./min.	1.4	1.4		0.3	0.3	0.6	1.1		1.0	1.3	1.6	1.4	1.4
$U_{OSM.}$ mosm./L.	497	494		357	350	368	397		374	399	410	447	412
$T^c_{H_2O}$/GFR	0.05	0.06		0.02	0.02	0.03	0.05		0.03	0.04	0.05	0.05	0.06
$U_{Na}V$ mEq./min.	0.1	0.1		0.4	0.4	0.4	0.4		0.5	0.5	0.5	0.3	0.06
T_{Na} mEq./min.	3.6	3.2		2.4	2.3	2.6	3.0		3.9	3.7	3.8	3.4	2.8
EF_{Na} per cent	2.8	3.0		14.3	14.8	13.4	11.8		11.4	11.9	11.6	8.2	17.6

Values other than E_{PAH} are means from five collections of urine.

of the hypertrophic segments, which measured 11 mm. Calyces were small in the atrophic segments. Those of the hypertrophied zones were grossly normal, as were also renal pelves, ureters, and main renal arteries. Upper poles of all 4 kidneys showed perirenal fibrosis in the areas of arterial clipping; the affected segmental arterial branches were patent.

Microscopic diagnoses in the 3 kidneys with severe polar atrophy were as follows: segmental ischemic atrophy with focal infarction in one; ischemic atrophy with glomerular hyalinization, interstitial fibrosis, and arteriolar thickening in one; and ischemic atrophy with focal interstitial round-cell infiltration in the third (Fig. 3). The fourth kidney differed in that polar atrophy was not severe. Microscopic findings included moderate tubular and glomerular atrophy, tubular dilatation, and capsular fibrosis extending irregularly into the immediate subcapsular cortical zone.

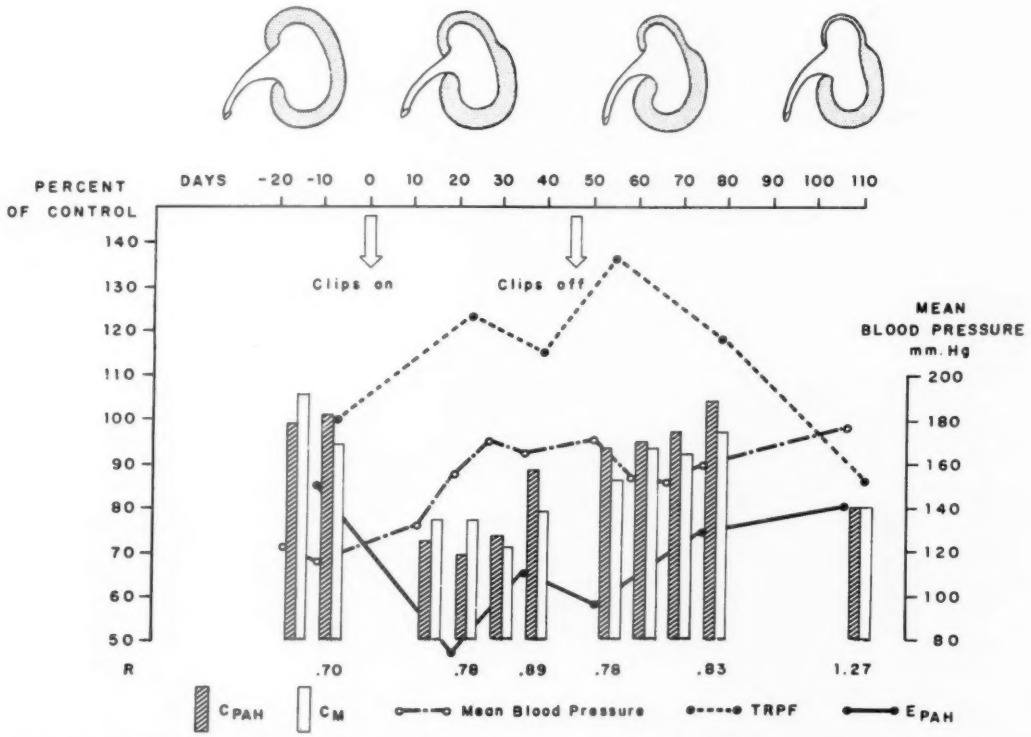

Fig. 1.—Observations after partial constriction of renal arterial branches. Values are means of observations in 4 dogs. Clearances are indicated as per cent of mean control levels. Figures on top show gross appearances of kidneys in the three experiments in which definite segmental atrophy was observed.

No arterial lesions were found in the pancreas and adrenals of the 2 dogs with the most extensive polar atrophy. The adrenals showed widening of the zona glomerulosa, such as has been described in experimental hypertension in rats[5] but not in dogs.

Excretory Functions.—

Renal plasma flow and glomerular filtration rate: ERPF (C_{PAH}) and GFR (C_M) were diminished equally—by about one-third—during the first 4 weeks

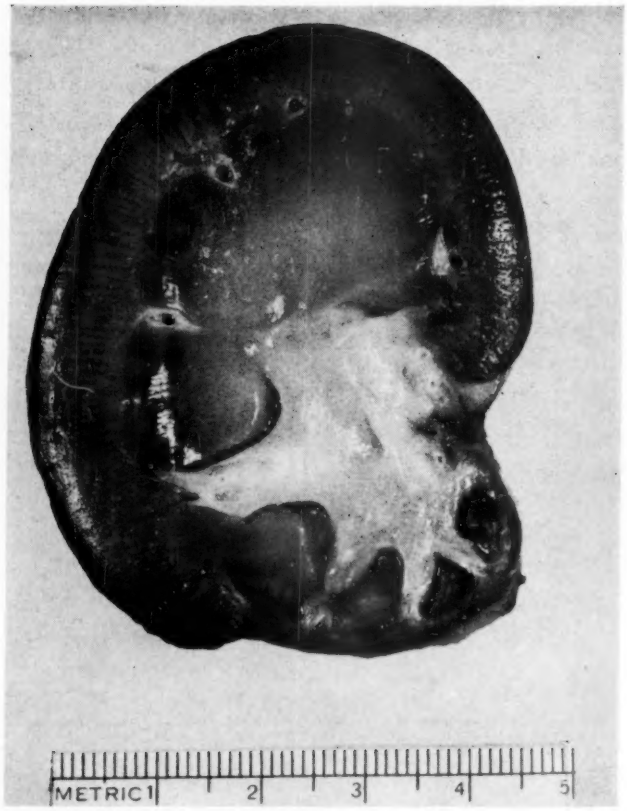

Fig. 2.—Gross appearance of kidney at autopsy (Dog 321); functional changes are listed in Table I.

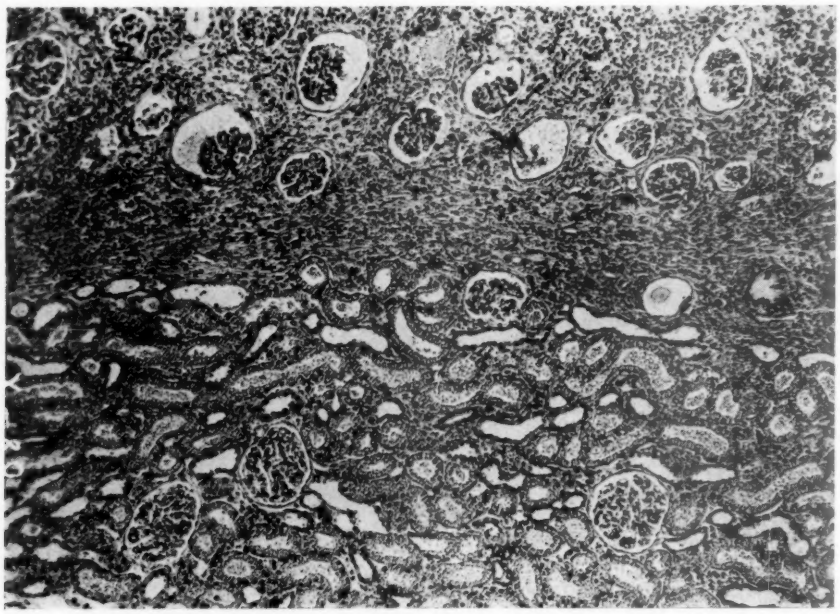

Fig. 3.—Autopsy specimen (Dog 321). Photomicrograph showing well-defined line of demarcation between atrophic (*upper*) and unaffected (*lower*) renal segments. In the atrophic segment, glomeruli are shrunken, more closely spaced, and exhibit membranous thickening; tubuli are absent in some areas, and severely degenerated in others. The interstice appears dense and shows patchy round-cell infiltrations. In the unaffected segment, a mild degree of tubular vacuolization is noted. Arterioles appear normal in both atrophic and normal segments. (Hematoxylin and eosin, ×80.)

after arterial constriction, and recovered to values four-fifths those of the controls at the sixth week. FF showed no consistent changes. Renal extraction of PAH, measured at the third and sixth weeks, was decreased; at these intervals TRPF and R were increased, and the ratio GFR/TRPF substantially decreased.

C_{PAH} further recovered one week after removal of the clips, and continued this trend toward normal for the next 4 weeks, but substantially decreased at the last observation. GFR recovered somewhat more slowly and sustained a similar late decrease. FF was not changed. E_{PAH} remained depressed one week after removal of the clips and was incompletely recovered at 5 weeks. Corresponding values for TRPF and R remained greater than control values; the ratio GFR/TRPF, low at one week, showed some recovery at 5 weeks.

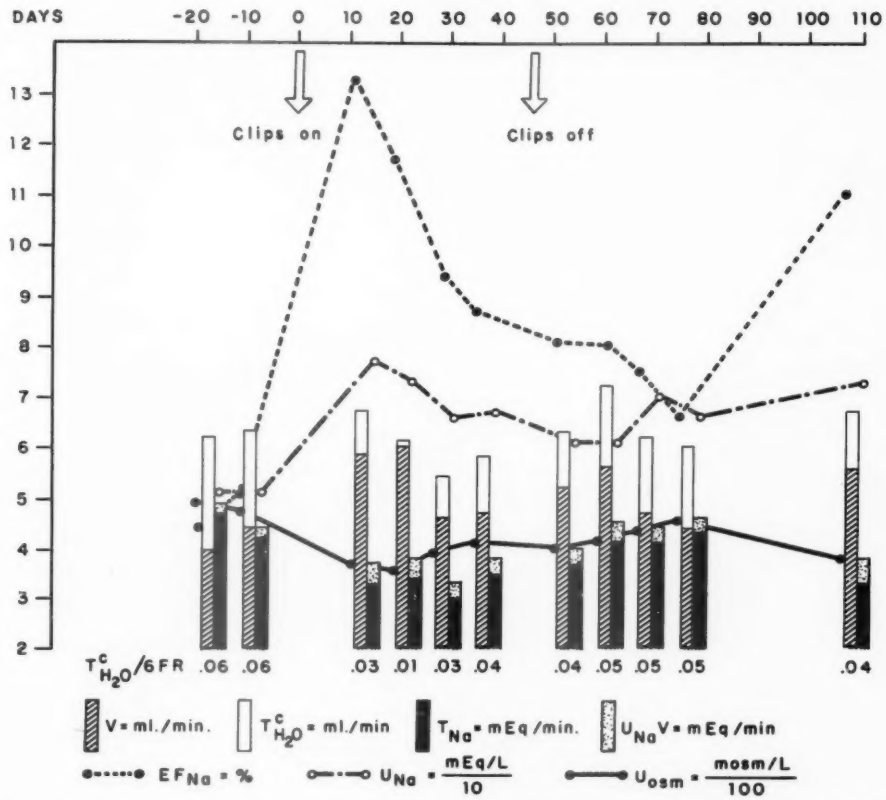

Fig. 4.—Observations after partial constriction of renal arterial branches in 4 dogs. Effects on water and sodium transport are demonstrated by mean values of five collecting periods.

At the time of the last observations, mean arterial pressures averaged 176 mm. Hg, and the blood urea content 61 mg./100 ml. Assuming that E_{PAH} was about 80 per cent, TRPF at this time would have been decreased to average 130 ml./min., or 86 per cent of control, representing a considerable decrease from previous levels.

Water and electrolytes (Fig. 4): Maximal water reabsorptive function ($T^c_{H_2O}$) was decreased by application of the clips, severely depressed at 3 weeks, and partially recovered during the following 3 weeks; recovery continued after

removal of the clips, but the function was again depressed at the last observation. A similar pattern of impairment, partial recovery, and eventual depression is shown when this function is expressed in relation to GFR as $T^c_{H_2O}/GFR$. During the period of arterial constriction, L_{Na} decreased in proportion to GFR, which it paralleled throughout the experiments. EF_{Na} was greatly increased one week after arterial constriction; it tended thereafter to recover but was still twice the value of the control at 6 weeks. Removal of the clips was followed by a continued trend of EF_{Na} toward control values. However, at the time of the last observation, EF_{Na} again increased, reflecting impairment as did other renal functions.

DISCUSSION

Hypertension and Renal Morphology.—Arterial hypertension and segmental ischemic atrophy persisted after removal of the arterial clips and in spite of demonstrably unimpeded arterial inflow. Hence, re-established perfusion of an ischemic, atrophic renal segment neither initiates morphologic regeneration nor relieves hypertension.

The reproducibility of control values of renal functions measured at varying intervals after uninephrectomy and at corresponding times prior to arterial constriction reflects maximal compensatory hypertrophy of the remaining kidneys at each interval prior to arterial clipping. Constriction of segmental arteries supplying about one fourth of the renal mass provided a second stimulus to renal growth to which the untouched, already hypertrophic segment responded with increases in mass and function, demonstrating a capacity for repeated response to appropriate renotrophic stimuli.

Failure of regeneration of the ischemic polar segments can be attributed to "irreversible" ischemic renal damage in the 3 cases of pronounced segmental atrophy, but this is less likely in the case showing less severe morphologic changes. A better explanation, since it applies to all 4 cases, is that after release of the arterial clips there was no further stimulus to renal growth, the stimulus having been previously fully exerted in provoking hypertrophy of the untouched portion of the kidney. Absence of a renotrophic stimulus is also suggested by the courses of renal functional changes, which were not notably affected by removal of the clips. The functional effectiveness of an active renotrophic stimulus is demonstrated by prompt partial recovery of excretory functions in clamped anuric, severely ischemic kidneys after removal of the contralateral normal kidney.[6]

The sequence of observations described would not accord with Braun-Menéndez'[2] concept of renal hypertension, which visualizes hypertension as an alternative response to circulating renotrophin in any situation in which the normal response, tissue growth, is somehow inhibited or frustrated. According to this concept, removal of the clips should have been followed by regenerative hypertrophy of the atrophic segment and simultaneous regression of hypertension; alternatively the hypertension should have remitted before removal of the clips, as the renotrophic stimulus, having fostered hypertrophy of the untouched segment, subsided.

The tendency to intensification of hypertension, presumed renal ischemia, and uniform depression of renal excretory functions observed in the last tests remains unexplained and merits further study. The data indicate increased renal vascular resistance and vasoconstriction with secondary diffuse renal ischemia. The functional changes might be attributed to nephrosclerosis except that, as is usual in the dog, anatomic evidences of arteriolar disease seem insufficient to account for significant deterioration of renal function, which is therefore tentatively ascribed to vasoconstriction.

Renal Perfusion and Hypertension.—Dogs with renal hypertension due to partial occlusion of main renal arteries or perinephritis have demonstrated maintenance of normal values for total renal blood flow and for many excretory functions.[5, 8, 12, 16] These observations have led to the inference that renal ischemia is not in itself the effective stimulus in renal hypertension. However, these experiments have not excluded the presence of focal ischemic areas in the affected kidneys. In the present experiments, hypertension was elicited in uninephrectomized dogs by a situation in which less than one-fourth of the remaining kidney was ischemic and, with hypertrophy, more than three-fourths of it was actually hyperemic. Since then a normal total renal blood flow is not inconsistent with significant segmental ischemia, these observations add to the evidence that focal renal ischemia may be a primary stimulus in renal hypertension. They show also that a high ratio of ischemic to nonischemic renal mass is not a necessary factor.

Excretory Renal Functions.—The initial changes in C_{PAH} and GFR are consistent with decreased renal perfusion and filtration in the segments affected by constriction of segmental arteries. Their subsequent slow recovery is apparently independent of the presence of arterial clips and corresponds to observations made after partial compression of main renal arteries. This sequence has been attributed by some investigators[9, 12, 15] to vasodilation distal to the arterial clip. However, with branch constriction, concurrent depressions of PAH extraction, of filtration, of relative renal plasma flow, and of sodium and water reabsorptions with persistent regressive morphologic changes are more consistent with the view that excretory functions were nearly completely and persistently suspended in the affected segment. The progression toward recovery observed after application of the clips seems to reflect changes in function of the untouched, hyperemic, hypertrophying renal segments.

This assumption permits correlation of observed changes in water and electrolyte transport with previous observations in dogs. Both increased renal arterial pressure in an intact kidney[13] and increased GFR in an intact renal segment[1] are accompanied by large percentile increases in water and sodium excretion. This effect is attributed to an increase of solute load per functioning unit—indicated by increased $GFR/Tm_{glucose}$ or, less directly, C_{Osm}/GFR—beyond tubular reabsorptive capacity.[3] Our observations of greatly increased sodium excretion, increased urine volume, and decreased urine concentration immediately following incomplete constriction of renal arterial branches resemble those of Blake[1] following complete occlusion of renal arterial branches.

Gradual recovery of reabsorptive functions in the hypertrophying segments, such as was observed in our experiments, could result from either adaptation of the existing transport systems or from addition of new cellular units during hypertrophy of residual nephrons.

The pattern of impairment of concentrating mechanisms noted at the final observations 4 weeks later resembled that sustained immediately after constriction of the renal arterial branches. The course of the impairment of reabsorptive functions remains somewhat obscure except as it may be attributed to diffuse renal vasoconstriction and ischemia. Pyelonephritis was ruled out by histologic examination.

Clinical Implications.—The present experiments show that in the dog hypertension may result from inadequate perfusion of one-fourth of one remaining hypertrophic kidney. The experiments simulate certain clinical cases of occlusive branch lesions[7] in some of which hypertension was relieved by excision of the affected segment,[11] or by partial nephrectomy. Since, in uninephrectomized dogs, release of segmental arterial constriction failed to relieve hypertension, improve renal function, or restore normal morphology of ischemic, atrophic renal segments, it is unlikely that conservative measures such as repair or endarterectomy of segmental arteries would be effective in patients with hypertension due to lesions of comparable arterial branches. Resection of the atrophic renal segment would seem to be the procedure of choice in such cases. The fact that in most clinical cases the opposite kidney is intact should not affect this conclusion since the intact mate should even diminish any regenerative stimulus to the nonischemic segment.

From the aspect of diagnosis, unilateral occlusive lesions of renal arterial branches have inconstant relative effects on urine flow, osmolality, and sodium content. The present experiments clarify the mechanism of this finding by demonstrating that adaptative and—at least after contralateral nephrectomy—hypertrophic changes in nonischemic renal segments may more than compensate for the functional effects of segmental disease. These changes may obscure the effects of disease in such a way that ureteral urine may give no indication of the presence of arterial branch lesions. Indeed, in a single remaining kidney, hypertrophy and adaptation to segmental renal atrophy may *increase* sodium output and decrease osmolality. Also, maintenance of normal total renal blood flow in such a kidney would obscure such an indirect diagnostic procedure as a radioisotope renogram.

SUMMARY

Reversibility of hypertension and functional and morphologic changes consequent on partial occlusion of segmental renal arterial branches were studied in uninephrectomized dogs. The functional changes reflect initial severe impairment of the affected renal segments, with subsequent over-all recovery, attributable to adaptation or hypertrophy or both of the untouched segments. Removal of the arterial constriction did not relieve hypertension, promote morphologic recovery of the atrophic renal segments or increase renal functions,

which subsequently deteriorated, possibly as a concomitant to persistent hypertension and vasoconstriction. The observations suggest that reconstruction of diseased segmental renal arterial branches may not be effective in the relief of hypertension and postocclusive renal changes as such procedures are in occlusive lesions of main renal arteries. From the aspect of diagnosis, the experiments show that hypertrophy of the unaffected segments may obscure effects of arterial branch lesions on the composition of the urine.

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RISK OF MAJOR SURGERY IN PATIENTS WITH OLD MYOCARDIAL INFARCTION

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RECENT advances in medicine, anesthetic technique, and surgery, especially pre- and postoperative care, have brought the need for re-evaluation of the surgical risk in individuals who have had a myocardial infarction. This is particularly so since follow-up studies of those who survive a myocardial infarction show that the long-term prognosis should be optimistic. We made a 5-year follow-up study of 653 patients who lived more than 2 months after their first myocardial infarction. It showed that 65 per cent lived more than 5 years.[10] We also made a 10-year follow-up study of a similar group of 211 patients. It showed that one-third lived more than 10 years.[11] Moreover, 65 per cent of men who returned to work after their first myocardial infarction were still working after 5 years.[9]

The majority of the reports in the literature as to the surgical risk in arteriosclerotic or coronary artery disease fail to separate those who only had angina pectoris from others who had a myocardial infarction. The latter implies electrocardiographic or autopsy evidence of changes, since a definite diagnosis of myocardial infarction cannot be made otherwise.[8]

Table I is a summary of literature as to the surgical risk in myocardial infarction of those operated on at least 4 weeks after the onset. In a few cases the myocardial infarction may have occurred in the immediate preoperative period. There is reported a total of 186 patients who had 253 operative procedures with a 5.1 per cent operative mortality. The mortality was calculated on the basis of the total operative procedures. Not all of these reports are exactly comparable. The criteria for the diagnosis of myocardial infarction varied and the definition of major surgery was not always well defined. Some included both "major" and "minor" operations. In some reports the mortality rate was based on totals which included deaths not related to the heart. It is impossible to compare the preoperative state of the patients in the various reports.

This report is based on 50 individuals who underwent major surgery at least 4 weeks after the onset of their infarction. The cases were from the Louisville General Hospital (a municipal charity hospital) and private practice. Everyone had a thoroughly documented history of a myocardial infarction proved by electrocardiograms. The majority had electrocardiograms shortly before surgery and all showed abnormalities due to the infarction.

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TABLE I. SUMMARY OF LITERATURE

AUTHOR	YEAR	NUMBER OF PATIENTS	NUMBER OF OPERATIONS	NUMBER OF DEATHS	OPERATIVE MORTALITY (%)
Butler et al.[2]	1930	8	8	1	12.5
Hickman et al.[5]	1935	8	10	1	10.0
Morrison[7]	1948	25	37	3	8.0
Hannigan et al.[4]	1951	58	58	3	5.2
Lockhead et al.[6]	1954	15	30	1	3.3
Baker et al.[1]	1955	46	72	4	5.5
Dana and Ohler[3]	1956	26	38	0	0.0
Total		186	253	13	5.1

Table II gives the sex of the patients and the age at the time of the surgery. There were 43 men and 7 women, ranging from 46 to 86 years in age. The majority were in their seventh decade. Three-fourths of the patients were operated on within 6 years after the onset of the infarction. Three had surgery 12, 15, and 22 years afterward, respectively. Six patients had had a second myocardial infarction before surgery. There was a total of 64 varied surgical procedures. Thus, 14 patients underwent two operations. There were 6 operative deaths which could be related to the heart, all among the men. This is 9.4 per cent of the total number of operative procedures performed but 12 per cent of the cases. There was one death in the operating room; one in the recovery room; and two 24 and 48 hours, respectively, after the operation.

TABLE II. AGE AND SEX

AGE AT TIME OF SURGERY	MALE	FEMALE	TOTAL	DEATHS
40-49	1	0	1	0
50-59	11	3	14	1
60-69	17	2	19	4
70-79	13	1	14	0
80+	1	1	2	1
Total	43	7	50*	6

*Who underwent a total of 64 operations with an operative mortality of 9.4 per cent.

CLINICAL SUMMARY OF THE CASES IN WHICH DEATH OCCURRED

CASE 1.—B. F., an 80-year-old man, 2 years after a myocardial infarction had a transurethral prostatectomy performed under spinal anesthesia. He had auricular fibrillation and was in mild congestive failure. He died suddenly from respiratory collapse in the recovery room.

CASE 2.—A. K., a 68-year-old man, had an uncomplicated myocardial infarction 8 years before a gastrostomy for carcinoma of the stomach. Preliminary anesthesia was Pentothal; then nitrous oxide–oxygen and ether. He died on the operating room table, apparently from ventricular fibrillation.

CASE 3.—I. B., a 65-year-old man, 5 years after a myocardial infarction, had an unsuccessful embolectomy on the left popliteal artery. Gangrene of the leg ensued and a week later he had a mid-thigh amputation of the left leg under spinal anesthesia. He died one day later. Intermittent congestive heart failure had been present since the myocardial infarction.

CASE 4.—F. P., a 65-year-old man, had persistent atrial fibrillation and intermittent congestive heart failure following a myocardial infarction 4 years before surgery was performed on him. He died suddenly 24 hours after a suprapubic prostatectomy and the removal of a small adenocarcinoma of the bladder. The anesthetics used were Pentothal and nitrous oxide–oxygen.

CASE 5.—A. B., a 56-year-old man, had an uncomplicated myocardial infarction 2 years before a cholecystectomy for acute cholecystitis with cholelithiasis. Surgery was performed under spinal anesthesia. He died suddenly 2 days later.

CASE 6.—M. M., a 64-year-old man, had an uncomplicated myocardial infarction 6 months before an enteroenterostomy for carcinoma of the jejunum. The anesthetic agents were nitrous oxide and Pentothal. He died suddenly 2 days later.

Table III lists the operations performed. All were classified as major procedures. No attempt was made to determine the incidence of cardiovascular and respiratory complications. They were expected to be above the average since some of the patients had had active symptoms of congestive heart failure and coronary artery insufficiency.

TABLE III. OPERATIONS PERFORMED (PROCEDURES)

TYPE OF OPERATION	NUMBER
Transurethral resection of prostate	9
Cholecystectomy	11
Lumbar sympathectomy	3
Aortography	1
Subtotal gastric resection	1
Retropubic prostatectomy	4
Embolectomy femoral artery	1
Inguinal hernioplasty and orchiectomy	3
Bilateral inguinal herniorrhaphy	4
Transurethral resection bladder tumor	2
Appendectomy	4
Colostomy for diverticulitis	1
Enteroenterostomy for carcinoma of jejunum	1
Popliteal embolectomy	1
Mid-thigh amputation	4
Suprapubic removal carcinoma of bladder	1
Open reduction and fixation femur	2
Resection sigmoid colon for diverticulosis	1
Lobotomy	1
Reopen cranium to control hemorrhage	1
Bilateral orchiectomy for carcinoma of prostate	2
Gastrectomy	1
Left hemicolectomy	1
Suprapubic cystotomy	1
Colostomy—carcinoma of rectum	1
Lumbar aortectomy	1
Bilateral cervical cordotomy	1
Total	64

Table IV lists the type of anesthesia used. The majority of the surgeons preferred ether or a spinal anesthesia. This study does not warrant specific recommendations as to the most favorable type or method of administration of an anesthetic agent. In general, for individuals who have had a myocardial infarction, apprehension and fear, hypoxia, marked falls in blood pressure, and high spinal anesthesia must be avoided.

TABLE IV. TYPE OF ANESTHESIA USED

TYPE	TOTAL
Spinal	33
Ether	10
Nitrous oxide	1
Caudal	1
Local	1
Pentothal	3
Cyclopropane	1
Combined:	
Anectine drip + Pentothal	3
Nitrous oxide + Pentothal	10
Nitrous oxide + Demerol I.V.	1
	64

DISCUSSION

Sudden or relatively sudden death can occur at any time in an individual who has survived a myocardial infarction.[10] This poses the question as to whether the operation itself caused the death of any or all of the 6 patients in this report.

This study does not have controls. But others have found that the risk is only slightly greater than that incurred from similar surgical procedures on a comparable age group without heart disease.[4] On the other hand, while a previous myocardial infarction is not a contraindication for major surgery, each contemplated operation should be carefully considered and not lightly undertaken. Elective surgery should be postponed as long as possible. When undertaken the risk can be decreased by meticulous medical management, skilled anesthesia, and careful pre- and postoperative care on the part of the surgeon.

SUMMARY

A study was made of 50 patients who underwent 64 major surgical operations 4 weeks or more after an acute myocardial infarction. There were 47 men and 7 women, ranging in age from 46 to 86 years. There were 6 deaths; all were men and all died within 48 hours after the operation. This is 9.4 per cent of the total number of operative procedures. Three-fourths of the patients were operated on within 6 years after the myocardial infarction but one had his episode 12, another 15, and another 22 years before the operation.

Six patients had had two myocardial infarctions.

This study confirms the experience of other reports that myocardial infarction, after at least 4 weeks of treatment, need not of itself ban major surgery.

The myocardial infarction patient must be meticulously guarded against apprehension and fear, hypoxia, and marked falls in blood pressure.

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INFLUENCE OF SOME PHYSICAL FACTORS UPON OXYGENATION WITH A PLASTIC MEMBRANE OXYGENATOR

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A NEW type of oxygenator employing plastic membranes has been developed and used, both in experimental and clinical applications, in our center. Previous experience accumulated in the use of bubble and other types of oxygenators convinced us that the problem of the ideal oxygenator was still unsolved. Microscopic air embolism, need for large amounts of antifoaming agents, defibrination of the blood, and denaturation of the blood proteins are but a few of the problems encountered (and up to now only partially solved) when a direct contact between the blood and oxygen is the basic principle of an oxygenator. In an attempt to overcome some of these difficulties we have developed a new type of membrane oxygenator similar in many basic features to the membrane oxygenators developed by Kolff[2] and Clowes.[1] The design of the oxygenator has been published elsewhere.[3]

The purpose of this article is to report a series of studies on the influence of several physical factors upon the oxygenation of blood through membranes. The influence of humidity, temperature, and pressure of the oxygen, as well as the influence of the thickness of the membranes and of the speed of the blood flow, were evaluated. Furthermore, the permeability to oxygen of different types of plastic membranes was studied by means of a special apparatus.

THE OXYGENATOR

The apparatus used in this study is shown in Fig. 1. It consisted of a modification of an early model of our oxygenator in which the number of membranes was reduced to one. The original apparatus consisted of a number of membrane units arranged in parallel. Each unit was a large heat-sealed tube of thin polyethylene held flat under tension by means of a pair of aluminum stretching bars (Fig. 2). These bars were provided with holes which were fitted over pins in a basic frame. In this way each membrane unit was stretched flat under tension. A small tube was tied to the top opening for blood entry and another large tube was tied to the bottom opening for exit. To achieve an even distribution of blood each membrane unit had a pattern of baffles on its upper part. Converging lines at the lower end directed the blood to the exit tube. Single units of this type could easily be stacked one on top of the other and the entrance and exit tubes of each unit could then be fitted to an inflow and an outflow manifold. The entire apparatus was placed in a special box onto which oxygen was circulated. For the present study a single membrane unit was used.

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METHODS AND MATERIALS

Forty-five mongrel dogs were used for a total of 54 experiments. In a few instances a simple reservoir of canine blood was used. When dogs were used they were anesthetized with Nembutal intravenously, intubated, and connected to a mechanical respirator. This was done in an effort to avoid variations of the O_2 saturation of the blood of the dog during the procedure. During the course of the experiment blood pressure, venous pressure, and ECG were continuously followed on an oscilloscope and occasionally recorded on a Sanborn Poly-Viso. Rectal temperature was taken with an electric thermometer.

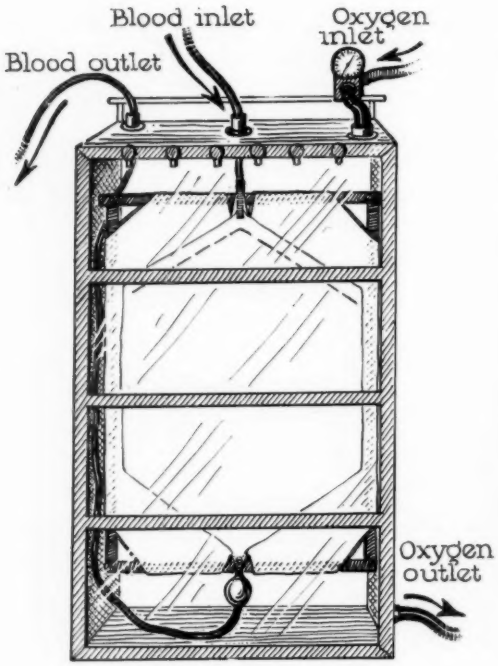

Fig. 1.

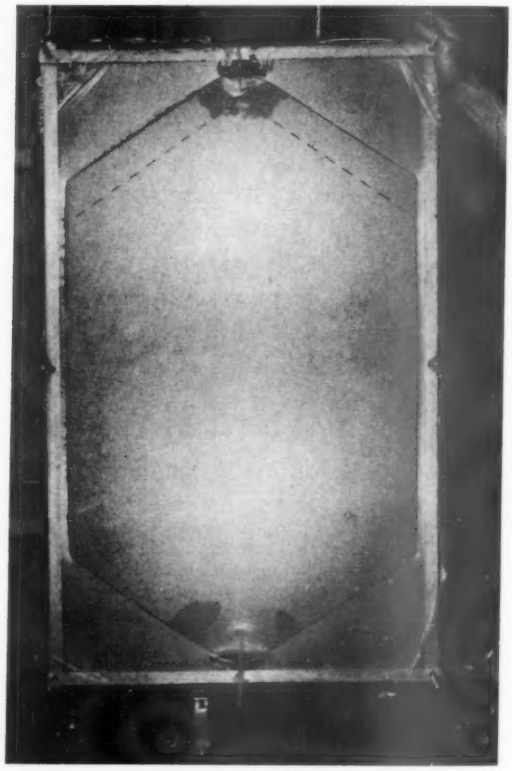

Fig. 2.

Fig. 1.—Semidiagrammatic drawing of the apparatus used for this study. Note the single membrane unit enclosed in a plastic box.

Fig. 2.—The single membrane unit (disposable) disconnected from the apparatus. Note the baffles on its upper part.

Arterial and venous blood samples were taken before and after each test and were subjected to gas analysis by the method of Van Slyke. The oxygen capacity, content, and saturation were determined in such a way on arterial and venous blood and the arteriovenous difference was calculated. Evaluation of the results was made by comparing the arteriovenous difference before and after the passage of the blood throughout the apparatus. A single membrane unit with a flow rate of 200 c.c. per minute was used. The diffusion of the oxygen through different types of plastic films was studied using the technique and the apparatus described by Shuman.[5]

PROCEDURE

After heparinization of the animal, plastic catheters of the largest possible diameter were introduced into the jugular vein and the carotid artery and connected, in order, with the venous and arterial line of the oxygenator. These maneuvers were conducted under clean, but not aseptic, conditions. The apparatus was primed with fresh heparinized blood to prevent "bleeding" of the dog into the oxygenator.

With the animal still connected to the respirator, a partial perfusion was started and carried out until the arterial and venous pressure and rectal temperature became stable. At this moment the test was started, changing the factor being tested as will be described for each particular type of experiment.

Five different groups of experiments were performed testing (1) the pressure of the oxygen, (2) the humidity of the oxygen, (3) the temperature of the oxygen, (4) the thickness of membranes, and (5) the speed of the blood flow through the membranes.

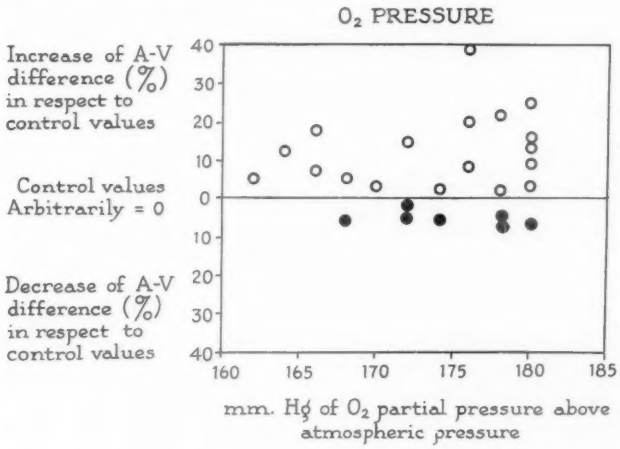

Fig. 3.

RESULTS

Oxygen Pressure.—In this experiment 26 tests were performed, employing 20 dogs for 22 different tests and, for 4 times, a simple reservoir of blood. After a few minutes of perfusion and when a stable level of venous and arterial pressure and of the rectal temperature was reached, two 5-minute periods of perfusion were timed and blood samples were collected before and after each one. In one period of perfusion the pressure of the oxygen into the plastic box was equal to the atmospheric pressure while in the other one it was increased to 180 mm. Hg above the atmospheric pressure. The low and high pressures were applied in a random fashion. The following results were obtained: In 18 cases a higher pressure of oxygen gave better oxygenation. On the other hand, in 7 instances better oxygenation was obtained with a lower oxygen pressure. In one case the results were similar. When a simple reservoir of canine blood was employed, thus excluding every interfering factor connected with the "status" of the dog, a higher oxygenation was constantly obtained when higher oxygen pressure was used. The results obtained are summarized in Fig. 3.

Thickness of Membranes.—In this study two different thicknesses of polyethylene membranes (0.0008 and 0.0004 inch) were used for each experiment. Ten experiments were performed with 8 dogs. After the balance of the arterial and venous pressures and rectal temperatures of the dog was achieved, the blood was run through the apparatus with the same general disposition as described previously. The blood samples were obtained after two subsequent 5-minute periods of partial perfusion in which the two types of membranes were used. The following results were obtained: In 9 cases a thinner membrane gave better oxygenation and in one instance the contrary was true.

Oxygen Temperature.—The influence of the temperature of the oxygen was tested in 9 experiments. Once more two 5-minute periods of partial perfusion were timed when conditions were stable. In one period (selected at random) the oxygen was at room temperature (about 28° C.); in the other, the oxygen was heated from 33° to 36° C. The results were as follows: Seven cases showed better oxygenation when oxygen at room temperature was employed; in one case better results were obtained with higher temperature; and in one case similar results were obtained. The results obtained are summarized in Fig. 4.

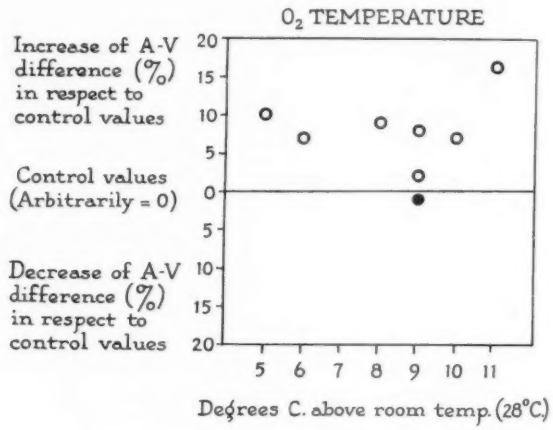

Fig. 4.

Transit Speed of the Blood Flow.—By tilting the apparatus at an angle of less than 90 degrees (upright position), a slowing of the blood flow through the membranes could be expected. This, in turn, would probably improve the distribution of the blood and subsequently improve the oxygenation. Since an angle of 30 degrees seemed to give the optimum of distribution, this angle was adopted and tested against the upright position. The influence of this factor was tested in 4 experiments employing 3 dogs. Two 5-minute periods of partial perfusion were timed. In one period the membranes were tested at an angle of 30 degrees (arbitrarily chosen), and in the other period they were in upright position. The following results were obtained: In 4 experiments better oxygenation was obtained when an angle of 30 degrees was employed. In one case the results were almost similar.

Humidity of the Oxygen.—This factor was tested in a short series of experiments employing 5 dogs. Once more two 5-minute periods of partial perfusion

were timed when conditions appeared to be stable. Samples of blood were obtained before and after the passage of the blood through the apparatus with high oxygen humidity (average of 74 per cent) and with low oxygen humidity (average of 50 per cent). The following results were obtained: In 4 cases higher oxygenation was obtained when a lower humidity was used. In one case the contrary was true.

Diffusion of the Oxygen Through Various Membranes.—In order to detect the best possible material in regard to the permeability of the oxygen, the apparatus originally described by Shuman was built and different types of plastic membranes were tested with it.

Fig. 5.—The apparatus originally described by Shuman[5] and built in our laboratory used to test the permeability of different types of plastic membrane to oxygen.

In this apparatus (Fig. 5) the test is made under the condition of atmospheric pressure of the gas (O_2 in this case) on one side of the membranes tested, and near-zero pressure of all gases on the other side. The index of permeability of the membrane is given in terms of cubic centimeters of gas transmitted per 100 square inches of surface per 24 hours. Such a figure is obtained from the following expression:

$$\frac{P}{760} \times V \times \frac{273}{T} \times \frac{100}{A} \times \frac{24}{\text{hours}}$$

where P = the absolute pressure inside the apparatus as measured in centimeters,

V = total volume of the inside of the apparatus in cubic centimeters,
T = temperature in degrees absolute,
A = surface area of test sample in square inches,
hours = time of test.

With the apparatus built in our workshop the above values are:

V = 2.77 cm.^{3}
A = 9.6 cm.^{2}
At a temperature of 27° C., T = 300° absolute.

Substituting these values in the equation we have the following working formula: P/hr. × 0.6 = c.c. of O_2 transmitted/100 sq. in./24 hr. In this way different types of polyethylene membranes of various thickness and physical quality, as well as other types of plastic films, were tested. The results listed in Table I were obtained.

TABLE I

	MEMBRANE	THICKNESS (INCHES)	AVERAGE VALUE
A	Polyethylene (Brand A)	0.001	1,371
B	Polyethylene (Brand B)	0.001	1,825
C	Polyethylene (Brand C)	0.001	1,063
D	Polyethylene (Brand D)	0.001	1,207
E	Silastic	0.0072	8,899
F	Silicone Rubber	0.0066	10,005
G	Mylar	0.0016	2,147
H	Cellophane	0.0015	479.55

DISCUSSION

The results achieved in this series of pilot studies were directly employed in the design of our membrane oxygenator. In our previous models, in fact, a heating system for both the blood and the oxygen was provided and an oxygen humidifier was used. The heating system was used in an attempt to avoid changes in the body temperature of the animal subjected to extracorporeal circulation and because the diffusion of gases through plastic membranes is higher with higher temperatures. As it has been shown, a higher oxygenation has been obtained when the oxygen was not preheated. This is in accordance with the oxygen dissociation curve of hemoglobin, which shows that an increase in temperature decreases the capacity of oxygen fixation. In view of this fact, the heating system has now been dropped in our latest oxygenator. However, a heat exchanger has been added to the circuit so that the temperature of the blood returning to the subject can be modified at will. In this way, when operating at normal temperature, it is possible to compensate for the loss of heat due to the circulation of the blood through the apparatus. On the other hand, hypothermia can be rapidly induced by lowering the temperature of the fluid circulating around the blood within the heat exchanger.

In the early apparatus an oxygen humidifier was used on the basis of a study published by Simiril and Hershberger.[6] According to these authors the permeability of cellulose and plastic films to oxygen (and other gases) can be increased by increasing the water content of the film. Our results, however, did

not confirm the afore-mentioned findings and therefore the oxygen humidifier is no longer present in our oxygenator. Perhaps this discrepancy in results might be due to the fact that in an oxygenator the situation is not quite the same as in a testing apparatus. In the latter, in fact, both surfaces of the membrane are in contact with a "dry" environment, while in the former one surface of the membrane is always in contact with a "wet" medium, namely, the blood.

In regard to the oxygen pressure, the following considerations must be pointed out. According to the results obtained it is desirable to have the highest pressure possible. This, however, can be achieved only at the cost of remarkable practical difficulties. The construction of a pressure box strong enough to hold high pressures and yet not unreasonably heavy is a rather difficult problem and the enclosure of the membranes in the box makes the handling of the whole apparatus difficult. Furthermore, even though in this way the partial pressure of the oxygen is increased, the partial pressure of the CO_2 will remain unchanged and therefore, the CO_2 diffusion gradient across the membranes is completely unaffected.

As described by Melrose[4] the CO_2/O_2 permeability ratio of polyethylene film is about 4; but the PO_2/PCO_2 partial pressure ratio on the side of the membrane opposite to the blood when pure O_2 is used is about 15. Therefore, there is a difference in the ratio of transport across the membrane which is already in favor of the oxygen. Consequently there is no need for a further increase of the oxygen diffusion gradient. What should be increased is the CO_2 diffusion gradient, but this obviously is not affected by any change in the partial pressure of the O_2. Considering that an oxygenator should provide both the addition of oxygen and removal of carbon dioxide, it is clear that by increasing the partial pressure of the oxygen only one aspect of the problem will be affected. Therefore, in our latest model such a box has been eliminated and the oxygen circulates between the membranes at atmospheric pressure. Regarding the type of plastic membrane one should use, from a theoretical point of view, other types than polyethylene are recommended. At present we are employing polyethylene membranes in our oxygenator mainly for practical reasons such as low cost, easy availability, and easy handling. However, studies are in progress in our laboratory for using routinely other types of plastic material which were observed to have a higher oxygen transmission index.

SUMMARY

A series of experiments to determine the influence of the pressure, humidity, and temperature of the oxygen as well as the position and thickness of the membranes on oxygenation with a membrane oxygenator, has been carried out.

It has been demonstrated that (1) higher oxygen pressure and temperature, (2) a lower oxygen humidity, (3) an angulation of the apparatus at 30 degrees leading to a prolongation of the transit time of the blood through the membrane, and finally (4) the thinnest possible membrane give better oxygenation. These principles have guided the design and construction of our latest model of oxygenator.

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EXPERIMENTAL APPRAISAL OF THE AGENTS EMPLOYED AS ANGIOCARDIOGRAPHIC AND AORTOGRAPHIC CONTRAST MEDIA

I. Neurotoxicity

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An ever-increasing number of reports have exposed the existence of adverse reactions resulting from clinical application of the contrast materials currently employed for angiocardiography and aortography. Many of the more serious of these complications have been the result of insult of the contrast agents to the central nervous system. It seemed appropriate therefore to undertake an experimental evaluation of the neurotoxicity of the commonly used angiocardiographic and aortographic contrast media.

METHOD

Sodium iodide (54.6 per cent), Urokon (70 per cent), Neo-Iopax (75 per cent), Miokon (90 per cent), Diodrast (70 per cent), Hypaque (90 per cent), and Thorotrast (25 per cent) were subjected to the evaluative procedures herein described. The substances innumerated represent the more readily available contrast media in the highest concentrations currently marketed, with the exception of sodium iodide (54.6 per cent). The concentration of sodium iodide chosen for use in this study is such that its iodine content is comparable to the iodine content of the organic iodide contrast media tested.

Unselected adult mongrel dogs were used as the test animals for assessing the neurological responses to aortic dissemination of the angiographic contrast solutions. Anesthetization was accomplished by the intravenous injection of veterinary Nembutal (30 mg. per kilogram) except in two instances in which succinylcholine immobilization was employed. The animals were placed in the supine position and the abdominal aorta was exposed by laparotomy with sterile precautions. The aortic instillation of the test contrast materials was performed as follows: The tip of a No. 18-gauge needle was slanted cephalad after puncture of the anterior wall of the aorta 1 cm. below the origin of the left renal artery and 15 c.c. of contrast medium were manually injected over a 5-second period (Fig. 1). No animal was included in this analysis if there was evidence of incomplete intraluminal delivery of the contrast material.

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Central nervous system tissue toxicities were measured in terms of the clinical evidences of abnormal neurological function. Spinal cord insult in the test animal was quantitated on the basis of clinical observations taken from the time of injection of the contrast material until demise or sacrifice of the animal. The immediate postinjection (during anesthesia) assessment was based upon the absence or presence of abnormal hindlimb motor responses. The absence or presence and quality of residual (postanesthesia) hindlimb motor deficits were determined and catalogued for each hindlimb immediately upon recovery from anesthesia and by means of serial neurological evaluation of the defective animals during their postinjection survival period. No neurologically incompetent animal was sacrificed until a minimal follow-up period of 3 weeks had elapsed. Animals exhibiting no neurological deficit were released after a minimum follow-up period of one week.

Using routine hematoxylin and eosin staining technique, histologic examination of tissue from the spinal cord was performed in selected instances.

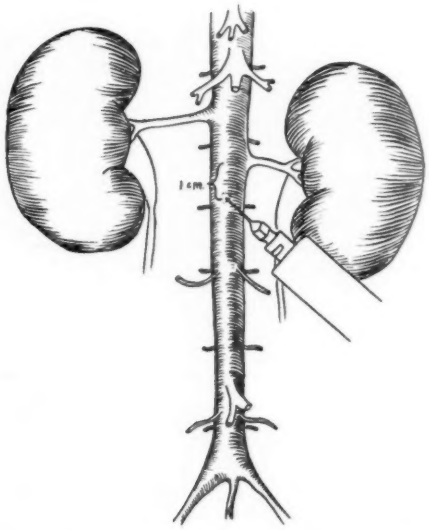

Fig. 1.—Illustration depicting site and technique of intra-aortic dissemination of contrast materials.

RESULTS

Sixty-one dogs of varying weights were utilized under the conditions of this study. The central nervous system damage was limited primarily to the spinal cord, although, as will be mentioned, a general cerebral depressive effect which, in its extreme form promptly resulted in death, was noted in some animals. The clinical expression of the spinal cord damage seemed naturally to divide itself into two main areas, namely: the immediate response to injury noted while the animal was still anesthetized and the postanesthetic neurological deficits exhibited by the test animals.

Hyperirritability phenomena manifested by the hindlimbs of the anesthetized animals formed a basis for the evaluation of the immediate toxic effect of the injected contrast materials upon the spinal cord. Three distinct components

of this hyperirritability complex permitted objective tabulation. The incidence and severity of these component reactions varied with the contrast material used and each component also demonstrated to some degree independence with regard to appearance. Spontaneous hyperextension, spontaneous sustained hindlimb myoclonic seizure and an exaggerated hindlimb motor response to external stimuli (hyperreflexia) were the three measurable elements of neuronal hyperirritability.

Hindlimb hyperextension, when present, was the earliest manifestation of neuronal irritability usually appearing within 5 to 90 seconds after the injection of the contrast substance. The clinical picture was that of sudden rigid hindlimb hyperextension sustained for periods lasting from 10 seconds to 2 minutes. Specifically, those animals tested with sodium iodide exhibited hyperextension which was characterized by an earlier onset and a shorter duration than was observed with the same phenomenon occasioned by the injection of the organic iodide test materials. Termination of the phase of hyperextension was signaled by either the onset of a myoclonic seizure or a gradual lysis of the rigidity and conversion to a flaccid state. Of the test contrast materials used, Thorotrast and Miokon failed to engender a hyperextension reaction, while the other end of the scale was illustrated by the sodium iodide group in which every animal exhibited the phase of hindlimb hyperextension (see Tables I through VII).

TABLE I

HINDLIMB NEUROLOGIC RESPONSE TO THOROTRAST

Animal Number	Weight (Kgm.)	ANESTHETIC PERIOD			POST-ANESTHETIC FOLLOW-UP			
		Hyper-extension	Seizure	Hyper-reflexia	Immediate	1 wk.	2 wks.	3 wks.
719	12.8	-	-	-	◐	◐	—	—
720	8.4	-	-	-	◐	◐	—	—
847	13.5	-	-	-	◐	◐	—	—
848	16.5	-	-	-	◐	◐	—	—
850	13.7	-	-	-	◐	◐	—	—
852	13.7	-	-	-	◐	◐	—	—
858	10.3	-	-	-	◐	◐	—	—
873	10.0	-	-	-	◐	◐	—	—

KEY: (Each hemicircle represents one hindlimb)

◐ = no motor deficit ● = paralysis

◍ = paresis † = non-survival

A correlation between the presence of hyperextension and the sequential appearance of another of the manifestations of neuronal hyperirritability was uniformly positive in the animals receiving Urokon, Diodrast, and Hypaque; the reverse of this situation occurred in the sodium iodide and Neo-Iopax animals where hindlimb hyperextension was the only detectable evidence of neuronal hyperirritability.

Spontaneous sustained myoclonic seizures constituted the most dramatic indication of neuronal irritability. The seizures appeared with stark suddenness within a period of 30 seconds to 2 minutes following instillation of the test material into the abdominal aorta, and were observed to have a variable duration of from one-half to 10 minutes. The convulsive movements were of a sustained

TABLE II

HINDLIMB NEUROLOGIC RESPONSE TO HYPAQUE

Animal Number	Weight (Kgm.)	ANESTHETIC PERIOD			POST-ANESTHETIC FOLLOW-UP			
		Hyper-extension	Seizure	Hyper-reflexia	Immediate	1 wk.	2 wks.	3 wks.
477	15.4	-	-	-	◑	◐	—	—
478	7.2	+	-	+	◐	†	—	—
764	11.0	-	-	+	◐	◐	—	—
765	12.8	-	-	+	◐	◐	—	—
775	13.2	-	-	-	◐	◐	—	—
791	10.0	-	-	-	◐	†	—	—
792	8.1	-	-	+	◐	◐	—	—
795	8.0	-	-	-	◐	◐	—	—

KEY: See Table I

TABLE III

HINDLIMB NEUROLOGIC RESPONSE TO DIODRAST

Animal Number	Weight (Kgm.)	ANESTHETIC PERIOD			POST-ANESTHETIC FOLLOW-UP			
		Hyper-extension	Seizure	Hyper-reflexia	Immediate	1 wk.	2 wks.	3 wks.
141	13.4	-	-	+	◑	◑	◐	—
145	17.0	+	-	+	●	◐	—	—
146	13.6	+	-	+	◑	◐	—	—
156	13.0	-	-	+	◐	◐	—	—
157	6.6	-	-	+	●	†	—	—
169	10.1	-	-	-	●	●	◐	—
516	9.0	-	-	+	●	◑	◑	◐
517	9.2	-	+	+	†	—	—	—
619	13.5	-	-	+	◑	◐	—	—

KEY: See Table I

rhythmical and forceful character, and involved only the musculature of the abdomen, hindlimbs, and tail. Urokon and Diodrast were the only two test substances followed by seizures (Tables III and VI). The seizures were invariably succeeded by hyperreflexia, the third of the three components of the neuronal hyperirritability complex.

Hyperreflexia not only followed the myoclonic seizures, but occasionally succeeded an initial hyperextension, and often was the sole expression of neuronal hyperirritability. In its milder form the hyperreflexia existed as an exaggerated deep tendon reflex capable of responding briskly to a gentle finger tap of the hindlimb. The severe counterpart of this mild reaction was usually noted to follow the myoclonic convulsions and was of such magnitude that a

TABLE IV

HINDLIMB NEUROLOGIC RESPONSE TO MIOKON

Animal Number	Weight (Kgm.)	ANESTHETIC PERIOD			POST-ANESTHETIC FOLLOW-UP			
		Hyper-extension	Seizure	Hyper-reflexia	Immediate	1 wk.	2 wks.	3 wks.
15	7.6	-	-	-	◑	◑	◑	—
105	7.6	-	-	-	†	—	—	—
124	10.0	-	-	-	◑	◑	—	—
125	9.0	-	-	-	◒	◒	◑	◑
127	10.3	-	-	+	●	●	◒	◒
140	16.5	-	-	-	◒	◒	◒	◑
402	7.1	-	-	+	†	—	—	—
403	12.2	-	-	-	●	●	●	●
498	15.4	-	-	-	◒	◑	◑	—
979	9.3	-	-	+	●	●	●	●

KEY: See Table I

TABLE V

HINDLIMB NEUROLOGIC RESPONSE TO NEO-IOPAX

Animal Number	Weight (Kgm.)	ANESTHETIC PERIOD			POST-ANESTHETIC FOLLOW-UP			
		Hyper-extension	Seizure	Hyper-reflexia	Immediate	1 wk.	2 wks.	3 wks.
168	10.5	+	-	-	◕	◒	◑	◑
175	13.6	+	-	-	◕	◒	◒	◒
176	15.0	+	-	-	●	†	—	—
190	11.6	-	-	-	◒	◒	◑	◑
191	13.6	+	-	-	●	●	†	—
198	9.0	+	-	-	●	†	—	—
695	9.9	+	-	-	●	†	—	—
696	10.6	+	-	-	●	●	†	—

KEY: See Table I

minimal external stimulation (that is, the dropping of a gauze sponge on the hindlimbs) often precipitated a short-term recrudescence of the preceding myoclonic seizure pattern. The duration of the period of hyperreflexia varied from 2 to 30 minutes with a rough correlation noted between severity and duration. Often suture closure of the abdominal wall of the experimental animal

had to be purposely delayed until the animal had become refractory to such stimulation, because approximation of the tissues was impossible under the conditions of extreme irritability which existed.

TABLE VI

HINDLIMB NEUROLOGIC RESPONSE TO UROKON

Animal Number	Weight (Kgm.)	ANESTHETIC PERIOD			POST-ANESTHETIC FOLLOW-UP			
		Hyper-extension	Seizure	Hyper-reflexia	Immediate	1 wk.	2 wks.	3 wks.
417	8.7	+	+	+	●	●	●	†
418	10.5	-	-	+	●	†	—	—
615	8.0	+	+	+	●	†	—	—
623	14.8	+	+	+	●	●	●	●
630	8.0	+	+	+	●	†	—	—
643*	12.3	+	+	+	†	—	—	—
670	18.5	+	+	+	●	†	—	—
689**	10.0	-	-	-	●	†	—	—
713**	8.6	-	-	-	●	†	—	—

KEY: See Table I

*Death attributed to bronchial aspiration.
**Succinylcholine immobilization.

TABLE VII

HINDLIMB NEUROLOGIC RESPONSE TO SODIUM IODIDE

Animal Number	Weight (Kgm.)	ANESTHETIC PERIOD			POST-ANESTHETIC FOLLOW-UP			
		Hyper-extension	Seizure	Hyper-reflexia	Immediate	1 wk.	2 wks.	3 wks.
199	15.0	+	-	-	†	—	—	—
219*	9.5	+	-	-	†	—	—	—
220	10.5	+	-	-	†	—	—	—
237	13.5	+	-	-	†	—	—	—
238	11.5	+	-	-	†	—	—	—
244	8.4	+	-	-	†	—	—	—
245	10.0	+	-	-	†	—	—	—
423	10.1	+	-	-	†	—	—	—
424	9.7	+	-	-	†	—	—	—

KEY: See Table I

*Death attributed to bronchial aspiration

No evidence of hyperreflexia was observed in the animals tested with sodium iodide, Neo-Iopax, or Thorotrast. The phenomenon was most prevalent in the Urokon and Diodrast groups.

In addition to the above recorded evidence of central nervous system injury certain other less easily quantitated immediate phenomena reflecting neuronal insult were observed.

Contraction of the spleen and tachycardia usually attended the injection of the test materials. Spasm and increased peristaltic activity of the intestine, detrusor muscle contraction occasionally associated with micturition, and defecation also frequently followed the injection of the contrast media. These responses appeared to represent mass autonomic discharge occasioned by noxious effects of the contrast substance and occurred particularly following the use of sodium iodide and to a lesser degree following Urokon and Neo-Iopax.

Animals under light pentobarbital anesthesia manifested an apparent deepening of their anesthetic level within seconds of completion of the aortic dissemination of the contrast media, primarily Urokon. The potentiation of anesthesia was of such a magnitude that it was considered desirable to administer Urokon during light anesthetic levels in order to avoid an inordinately high anesthetic mortality rate.

No immediate (within 12 hours) postinjection death could be clearly attributed to anesthetic error, and, therefore, failure to regain consciousness was considered an indication of the magnitude of the neurotoxic potential of the injected contrast agent except in the two animals, one in the sodium iodide group and one in the Urokon group, that expired from complications resulting from bronchial aspiration of gastric contents while under anesthesia (see Tables VI and VII). On this basis the injection of sodium iodide was uniformly followed by death within the first few hours without the animal's ever regaining consciousness. The administration of Miokon in two instances and of Diodrast in one instance led to a similar demise of the injected animals.

Thus, of the original group of 61 animals, 48 survived both injection and anesthesia for a length of time sufficient to permit objective evaluation of hindlimb motor deficits. Therefore, each of the contrast agents (except sodium iodide) was objectively evaluated on the basis of findings in an equal number of surviving animals, namely, eight.

Paraplegia represented the ultimate in hindlimb motor deficiency. The clinical syndrome was that of a flaccid paralysis of the hindlimbs and tail with associated sphincteric incontinence leading to maceration and ulceration of the integument of the denervated parts. Sensory modalities were inhibited from the paralyzed areas as painful stimuli were ignored by the affected animals. Priapism compounded this paraplegic state in two instances (one animal in each of the Urokon and Neo-Iopax groups) and was itself in turn complicated by the development of gangrenous changes of the phallus in one animal (Urokon).

Urokon fostered paraplegia in all 8 test animals receiving this substance. Five of the Neo-Iopax group and two of the Miokon group were similarly rendered paraplegic (see Tables IV, V, and VI). Of the 15 animals manifesting paraplegia, none exhibited evidence to indicate a return of any voluntary motor activity. In one animal the flaccid paraplegia gradually evolved into a spastic paraplegia.

Lesser degrees of spinal cord damage as measured by clinical examination were revealed by unilateral paresis, bilateral paresis, or unilateral paresis in

conjunction with unilateral paralysis. These intermediate degrees of motor deficit were observed in 16 animals. The less severe deficits occurred with varying frequency as a result of injections of Neo-Iopax, Miokon, Diodrast, and Hypaque (Tables II through V).

Priapism, anesthesia, skin ulceration, and impaired sphincter function did not occur in animals not paraplegic. A further contrasting feature between paraplegic and paretic animals was the tendency of the latter group to show amelioration of their deficits with the passage of time (10 animals complete recovery and 5 animals partial recovery).

All 8 animals receiving Thorotrast, 7 animals receiving Hypaque, one animal receiving Diodrast, and one animal receiving Miokon did not sustain spinal cord damage as evidenced by their failure to display any clinical reflection of neuronal insult.

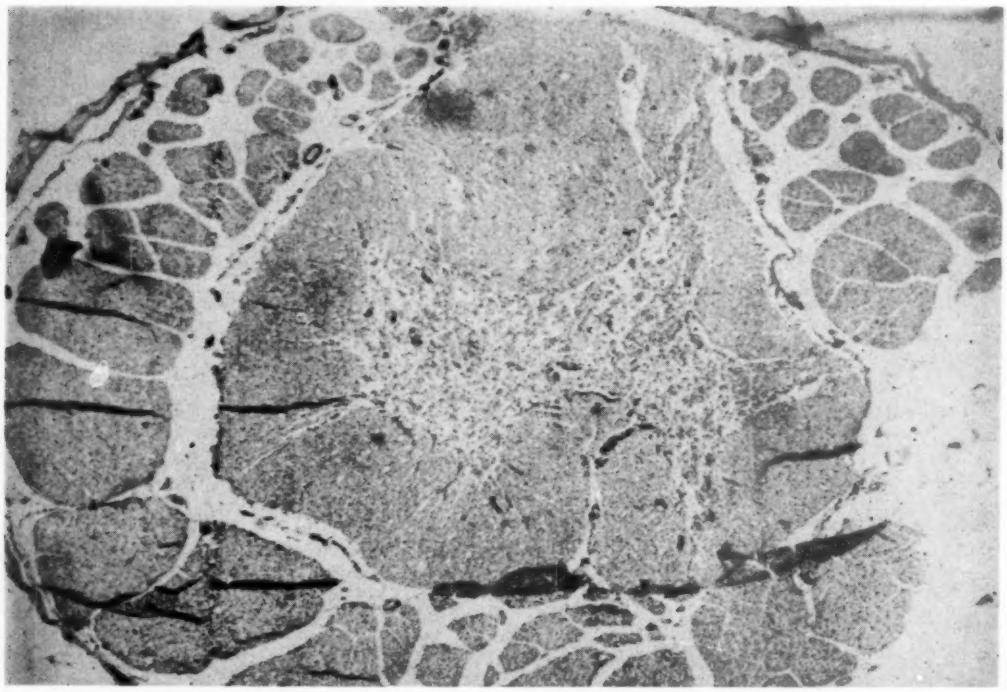

Fig. 2.—Low-power photomicrograph showing selective destruction of gray matter of the sacral region of the spinal cord taken from an animal rendered paraplegic by Urokon.

Fifteen of the 48 animals that survived anesthesia died during the post-anesthetic observation period. Five of these deaths occurred in animals exhibiting progressive azotemia secondary to concomitant renal damage. At autopsy, peritonitis was found in two other instances. Only complications of the neurological injury could be implicated as the cause of the early demise of the other 8 animals.

Spinal cords from animals that demonstrated paraplegia were found, when subjected to histologic analysis, to display massive dissolution of the gray matter (Fig. 2).

DISCUSSION

Proof that central nervous system damage resulting from the injection of angiographic contrast material constitutes a recurring and serious hazard to the patient is offered by the prominent consideration given this complication by those reviewing the subject.

Central nervous system damage can be incriminated in 13.5 per cent of the fatal complications of abdominal aortography, 24 per cent of the fatal complications of thoracic aortography, and 48 per cent of the fatalities resulting from angiocardiography.[1, 3, 11]

Neurological complications such as hemiplegia, blindness, convulsion, and paraplegia constitute 35 per cent of the severe nonfatal complications resulting from abdominal and thoracic aortography.[1, 11]

Although the ultimate nature of the neurotoxic mechanisms involved in the production of central nervous system damage by the contrast agents studied cannot as yet be described, certain qualitative aspects pertaining to the character of the central nervous system injury may be formulated. The neuronal damage observed subsequent to the aortic injection of the contrast materials studied is the result of a direct cellular insult rather than a secondary phenomenon incident to anoxia, vascular thrombosis, or capillary endothelial alterations. The intensity and quality of the toxic reactions vary in an as yet incompletely understood fashion with the chemical structure of the contrast agent. The clinical and histologic appraisal of central nervous system damage resulting from aortic dissemination of contrast media indicates that the injury is generally of a lasting destructive character rather than suppressive and temporal in nature (Fig. 2). Support of these statements may be derived from an analysis of the evidence obtained as a result of the series of tests described herein and other reports.[2, 4-10, 13]

No definitive attempt was made to control the weight factor, other than to avoid the use of extremely large or extremely small animals. The resulting mean weights for the seven groups of test animals were as follows: sodium iodide (10.9 Kg.), Urokon (11.0 Kg.), Neo-Iopax (11.7 Kg.), Miokon (10.5 Kg.), Diodrast (10.5 Kg.), Hypaque (10.1 Kg.), and Thorotrast (12.5 Kg.). It may be inferred, therefore, that weight per se did not influence the immediate or delayed response to the injected test material.

The appearance or absence of any or all of the components of the immediate motor response (hyperextension, seizure, and hyperreflexia) to the injected contrast media may be correlated with the hindlimb motor deficit observed in the postanesthetic period. Twenty-six animals exhibited at least one of the three immediate phenomena. Twenty-two of these animals subsequently demonstrated some loss of hindlimb motor function. Seizure was engendered by the contrast agent in five instances and was uniformly followed by paraplegia.

Only 7 of the 20 animals (excluding 2 animals immobilized with succinylcholine) that did not manifest any evidence of immediate motor response showed residual hindlimb motor function impairment upon recovery from anesthesia and only one of these 7 was paraplegic.

Thus, it would seem that the appearance of one or all of the immediate forms of motor response has definite prognostic significance in that residual motor deficit can be predicted in about 85 per cent of these instances; however, the converse, absence of hyperirritability, is no guarantee of subsequent normal motor function. Further, it may be stated that an immediate seizure augurs paraplegia as the definitive neurological deficit resulting from contrast media insult.

The general character of the components of the immediate motor response was similar no matter what the chemical structure of the inciting test material. The only variation from this was noted in the case of sodium iodide in which the hyperextension response appeared earlier and was of shorter duration than when manifested as a reaction to the injection of any of the other contrast substances.

The pattern of immediate motor response varied somewhat with the contrast media injected. Sodium iodide and Neo-Iopax aroused hyperextension generally in the absence of any of the other components of the immediate motor reaction. Miokon was noteworthy because of its peculiar inability to cause an immediate motor reaction in spite of a high incidence of residual hindlimb motor impairment.

The incidence and character of the hindlimb motor deficits demonstrable in the postanesthetic period have been described. The evolutionary changes, noted in the course of the hindlimb paresis and paralysis in the follow-up period, can be related to the severity of the initial hindlimb motor impairment. The animals that were initially paraplegic experienced no regression of their disease while all animals that exhibited original deficits less than paraplegia (and survived beyond one week) displayed evidence of progressive return of hindlimb motor function within 1 to 3 weeks.

The intensity of the visceral responses, previously referred to herein as a mass autonomic nervous system discharge, can be correlated with the neurotoxicity of the contrast agent employed in a fashion similar to mortality and spinal cord damage.

The seeming potentiation of barbiturate narcosis by Urokon in these animals has a clinical counterpart on the basis of the report by McAfee and Willson.[12]

CONCLUSIONS

The capability of the currently available angiocardiographic and aortographic contrast media for causing central nervous system injury is founded upon their cytotoxic effect which in itself is dependent upon their chemical structure.

The results of this study provide information which permits a grading of the neurotoxic potential of the seven contrast materials (in the concentrations employed) evaluated. Thus, a list based upon descending order of neurotoxicity can be formulated as follows: sodium iodide, Urokon (sodium acetrizoate), Neo-Iopax (iodomethamate), Miokon (sodium and methylglucamine diprotrizoate), Diodrast (iodopyracet), Hypaque (sodium and methylglucamine diatrizoate), and Thorotrast (thorium dioxide).

Realizing that various other factors (radiopacity, viscosity, facility of handling, and so on) may govern the selection of angiographic contrast media, we feel that in clinical situations allowing arbitrary choice of the angiocardiographic and aortographic contrast material a compound with minimal neurotoxic potential should be employed. Hypaque and Thorotrast on the basis of this study exhibit the least affinity for central nervous system tissues. Thorotrast, because of its relatively low radiopacity, propensity for engendering a local granulomatous reaction, and suspected cancerogenic role, is unsuitable for use except possibly in specific instances. Hypaque, on the strength of these considerations and its known adequacy for angiographic visualization, would appear to be the current contrast agent of choice for angiocardiography and aortography.

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STUDIES OF HEPATIC BLOOD FLOW AND OXYGEN CONSUMPTION DURING TOTAL CARDIOPULMONARY BYPASS

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CLINICAL observations of patients undergoing open heart operations with the aid of extracorporeal circulation have sometimes revealed definite but transient alterations in liver function as determined by the usual laboratory examinations. Hepatic anoxia, due to reduced cardiac output, has long been known to cause hepatocellular changes in both man and experimental animals. It was felt, therefore, that an experimental study might elucidate some of the factors contributing to alterations in liver function after cardiopulmonary bypass. In the present investigations hepatic blood flow and oxygen consumption were measured during a control period and during perfusion at systemic flow rates commonly employed in open heart surgery.

METHODS

Healthy fasting mongrel dogs weighing 12.4 to 22.9 Kg. were employed. The animals were anesthetized with 2 mg. per kilogram of morphine sulfate given intramuscularly followed in 20 to 30 minutes by 48 mg. per kilogram of chloralose and 480 mg. per kilogram of urethane also administrated intravenously. Ventilation was maintained by a mechanical positive pressure respirator. The right chest was opened through the fifth intercostal space, the venae cavae were exposed, the right pulmonary artery was dissected free, and the pericardium was widely incised. A second incision was made in the tenth intercostal space and extended through the right rectus muscle to the midline of the abdomen. The right hemidiaphragm was transected exposing the liver. The proximal portion of the inferior vena cava was cannulated through the right adrenal vein for pressure recordings. A braided silk ligature was passed around the inferior vena cava above the renal veins and the left adrenal vein. This ligature, when tied, interrupted the cava and separated the hepatic venous return from the remainder of the inferior caval flow (Fig. 1). Pressure in the portal vein was measured by means of a small cannula placed through a purse-string suture in that vessel. The peritoneal covering over the hepatic artery was divided longitudinally and care was taken to preserve the surrounding nerve plexi. The gastroduodenal artery was then ligated at its origin from the hepatic artery.

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Heparin (3 mg. per kilogram) was given intravenously and the previously exposed femoral artery was cannulated. Two small polyvinyl catheters were then placed proximally and distally in the hepatic artery and attached to a recording rotameter.[13] Another larger polyvinyl cannula was placed in the distal inferior vena cava through a stab wound just above the renal veins and held in place by means of a purse-string suture. Cannulation of the superior vena cava and the proximal or thoracic portion of the inferior vena cava was accomplished by large cannulae passed through the right atrium. In addition, a small thin-walled stainless steel cannula was placed proximally in the right pulmonary artery.

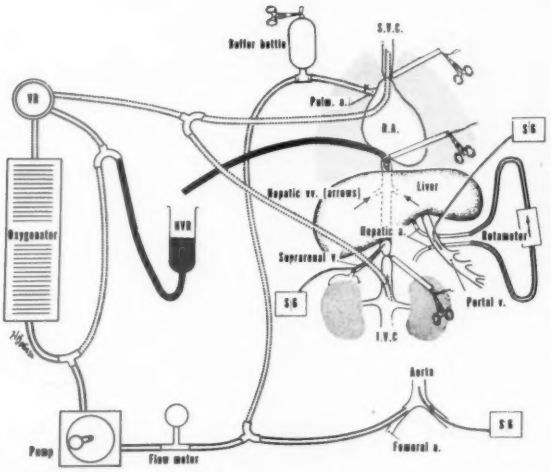

Fig. 1.—Diagrammatic illustration of the cannulation of the dog and the extracorporeal circuit. *HVR*, hepatic venous reservoir; *VR*, venous reservoir; *SVC*, superior vena cava; *IVC*, inferior vena cava; *SG*, Statham pressure transducer. For control studies venous blood bypassed the oxygenator but was pumped through the flowmeter into the pulmonary artery. For heart-lung bypass venous blood was oxygenated in the oxygenator and returned to the femoral artery.

The extracorporeal circuit was completed with a rotating disc oxygenator[8] with a single arm nonocculsive roller pump. Venous blood from the superior vena cava and distal inferior vena cava drained by gravity into a venous reservoir. Hepatic venous blood was drained from the thoracic inferior vena cava into a separate calibrated reservoir which in turn drained by gravity flow into the venous reservoir. Blood was collected during timed intervals in the hepatic venous reservoir for flow determinations. The temperature of the animals was maintained at normal levels by warming coils on the oxygenator. The pump-oxygenator was primed with blood obtained from donor dogs which had been lightly anesthetized with sodium Pentothal. The partial pressure of the oxygen in the blood at the arterial end of the oxygenator was monitored by a Clark oxygen electrode.[4] Ninety-nine per cent oxygen and 1 per cent carbon dioxide were added to the oxygenator at a rate equal to systemic arterial flow. Aortic and portal venous pressures as well as the pressure in the proximal inferior vena cava into which the hepatic veins drained were measured by Statham pressure transducers and recorded on a multichannel direct-writing

oscillograph. The pressure in the isolated proximal inferior vena cava was maintained between 0 and 5 mm. Hg by raising or lowering the open end of the cannula draining this segment.

When hepatic blood flow was determined during control periods, without complete cardiopulmonary bypass, venous blood did not enter the oxygenator but was pumped through the cannula of an electromagnetic flowmeter[11] and a buffer bottle into the right main pulmonary artery. Thus, with exception of the relatively small coronary flow, the flowmeter measured cardiac output indirectly. When studies were made during complete bypass, blood from the venous reservoir was diverted into the oxygenator and was then returned through the flowmeter to the femoral artery. A detailed schematic diagram of the experimental preparation is shown in Fig. 1.

Each period of study was of 20 minutes' duration and flows and pressures were recorded at 5-minute intervals. In 6 dogs during the fourth interval, when all parameters were stable, arterial, portal venous, and hepatic venous blood samples were drawn anaerobically for determination of oxygen content. These measurements were carried out by spectrophotometric or manometric techniques.[15, 17]

Hepatic blood flow and oxygen consumption were first measured during a control period when the dog's left ventricle was perfusing it at 2.8 ± 0.1 L. per minute per square meter of body surface area. After this determination cardiopulmonary bypass was initiated and similar studies were carried out at arterial flow rates varying between 2.8 ± 0.1 and 1.0 ± 0.1 L. per minute per square meter of body surface area. Body surface area was determined by use of a nomogram based on the animal's weight.[1]

Portal venous flow was determined by relating hepatic venous flow and hepatic arterial flow (PVF = HVF – HAF). Hepatic oxygen consumption was calculated by the equation:

$$\text{Hepatic } O_2 \text{ consumption (ml./100 Gm. liver)} = \frac{HAF \times HAO_2 + PVF \times PVO_2 - HVF \times HVO_2}{\text{Liver weight in grams}} \times 100$$

HAF = hepatic arterial flow, milliliters per minute.
HAO_2 = hepatic arterial oxygen content, volume per cent.
HVF = hepatic venous flow, milliliters per minute.
HVO_2 = hepatic venous oxygen content, volume per cent.
PVF = portal venous flow, milliliters per minute.
PVO_2 = portal venous oxygen content, volume per cent.

RESULTS

Total hepatic blood flow was determined in 12 dogs under the control conditions described above and during total cardiopulmonary bypass at various systemic flows. In the control period at a flow of 2.8 ± 0.1 L. per minute per square meter of body surface area, hepatic flow ranged between 19.7 and 57.5 ml. per minute per kilogram and averaged 32.6 ml. per minute per kilogram (Fig. 2). In 7 animals the liver was weighed and total hepatic blood flow could also be expressed as milliliter per minute per 100 Gm. of liver. These values ranged between 77.5 and 165 and averaged 111.2 (Fig. 3).

The relationships of total hepatic flow to systemic flow during cardiopulmonary bypass are shown in Figs. 2 and 3. At a systemic flow equal to that measured in the control period, hepatic flow was unaltered; the mean value was 33.4 ml. per minute per kilogram or 120.7 ml. per minute per 100 Gm. of liver. Reduction in systemic flow to 2.2 ± 0.1 L. per minute per square meter slightly reduced hepatic flow to an average of 29.4 ml. per minute per kilogram or 109.2 ml. per 100 Gm. of liver. Further reductions in systemic flow were accompanied by proportionate decreases in total hepatic flow and at 1.0 ± 0.1 L. per minute per square meter, this averaged only 12.9 ml. per minute per kilogram or 38.6 ml. per minute per 100 Gm. of liver.

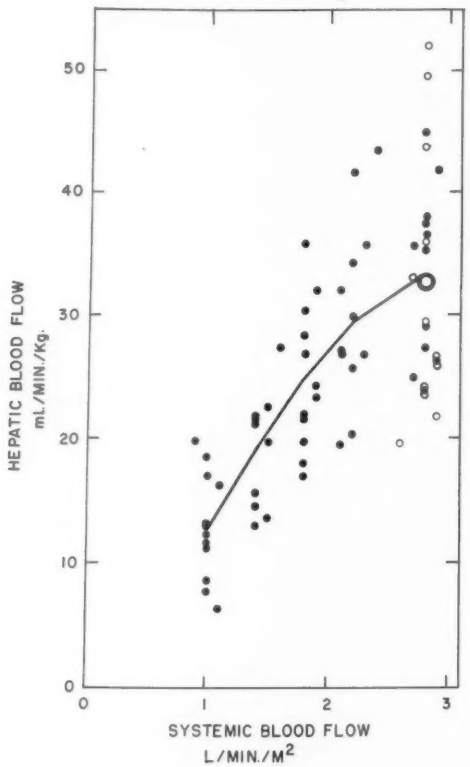

Fig. 2.—The relationship between hepatic blood flow and body weight of the dog is shown at a normal controlled cardiac output and at various systemic flows during cardiopulmonary bypass. Open circles = control flows; solid circles = flow during cardiopulmonary bypass; double circles = mean control flow. The solid line is mean flow during cardiopulmonary bypass.

The relative contributions of the hepatic artery and portal vein to total liver flow are shown in Fig. 4. Hepatic arterial flow decreased only slightly when systemic flow was reduced. At systemic flows of 2.8 ± 0.1 and 1.0 ± 0.1 L. per minute per square meter the hepatic arterial flows were 27.2 and 16.0 ml. per minute per 100 Gm. of liver, respectively. Decreases in portal venous flow, on the other hand, accounted almost entirely for the reduction in total liver blood flow which followed reductions in systemic flow.

The oxygen consumption of the liver was calculated from the formula presented (Table I). In the control period with the cardiac output 2.8 ± 0.1 L. per minute per square meter oxygen consumption averaged 5.0 ml. per 100

TABLE I

DOG				SYSTEMIC FLOW (L./MIN./M.²)	HEPATIC ARTERY FLOW (ML./MIN.)	PORTAL VEIN FLOW (ML./MIN.)	HEPATIC VEIN FLOW (ML./MIN.)	HEPATIC ARTERY O_2 CONTENT (VOL. %)	PORTAL VEIN O_2 CONTENT (VOL. %)	HEPATIC VEIN O_2 CONTENT (VOL. %)	TOTAL LIVER O_2 CONSUMPTION (ML./MIN.)	SPLANCHNIC O_2 CONSUMPTION (ML./MIN./100 GM. LIVER)	LIVER O_2 CONSUMPTION (ML./MIN./100 GM.)
NO.	WT. (KG.)	BSA (M.²)	LIVER WT. (GM.)										
15	22.5	0.89	470	2.8 control	155	430	585	14.8	13.5	8.1	33.6	8.2	7.2
				2.8	154	637	791	14.5	12.8	8.4	37.4	10.0	8.0
				2.2	159	611	770	14.1	10.2	7.0	30.8	11.4	6.6
				1.4	136	348	484	12.4	9.1	6.3	18.0	6.1	3.9
				1.0	136	136	272	13.6	3.0	2.0	17.1	6.6	3.6
17	18.5	0.78	570	2.8	179	496	675	10.1	8.7	4.9	28.2	6.2	5.0
				2.2	210	384	594	10.3	7.2	3.3	29.6	7.3	5.2
				1.8	182	344	526	10.4	7.2	2.7	28.4	7.1	5.0
				1.4	150	248	398	10.2	6.0	2.6	19.8	5.3	3.5
				1.0	106	194	300	10.2	7.2	1.9	19.0	4.4	3.3
18	15.5	0.69	358	2.2	30	272	302	14.6	10.4	4.2	19.9	5.6	5.5
				1.8	38	226	264	14.6	9.8	3.5	18.5	5.3	5.2
				1.4	38	186	224	14.6	10.3	4.7	14.2	4.0	4.0
				1.0	58	118	176	14.6	9.1	3.2	13.4	3.6	3.8
20	16.0	0.71	548	2.8 control	156	419	575	14.7	14.0	10.9	19.0	6.0	3.5
				2.8	128	472	600	15.1	12.8	7.1	37.0	8.7	6.8
				2.2	156	320	476	16.4	10.0	4.4	36.7	10.4	6.7
				1.8	133	217	350	17.0	4.8	3.5	20.7	8.6	3.8
				1.4	67	140	207	14.7	4.5	1.2	13.7	5.1	2.5
				1.0	77	59	136	14.4	7.0	1.2	13.6	3.3	2.5
22	13.7	0.64	387	2.8 control	95	205	300	16.3	13.7	8.2	19.0	6.3	4.9
				2.8	97	278	375	15.6	12.0	8.2	17.8	7.2	4.6
				2.2	100	268	368	15.9	13.2	9.3	17.1	6.3	4.4
				1.8	70	177	247	16.3	11.4	5.5	10.8	6.9	2.8
				1.4	43	146	186	16.1	10.8	5.7	11.6	5.0	3.0
				1.0	38	68	106	16.3	7.7	1.7	10.3	4.0	2.7
23	18.8	0.79	557	2.8 control	200	244	444	15.9	11.5	8.0	24.3	6.3	4.4
				2.8	169	376	545	16.1	11.3	8.2	25.1	7.7	4.5
				2.2	173	336	509	16.0	11.3	8.2	23.9	7.2	4.3
				1.8	142	268	410	16.8	10.6	6.8	24.3	7.4	4.4
				1.4	103	190	293	17.6	9.4	4.3	23.3	7.0	4.2
				1.0	67	51	118	17.2	5.7	2.0	15.2	3.2	2.7
Mean determination				2.8 control								6.7	5.0
				2.8								8.0	5.8
				2.2								8.0	5.5
				1.8								7.0	4.2
				1.4								5.4	3.5
				1.0								4.2	3.1

Gm. of liver per minute. During cardiopulmonary bypass at a similar flow rate it was 5.8 ml. per 100 Gm. per minute. At a perfusion rate of 2.2 ± 0.1 L. per minute per square meter oxygen consumption was not significantly altered, but at lower flows it decreased markedly and was only 3.1 ml. per 100 Gm. of liver per minute at a systemic flow rate of 1.0 ± 0.1 L. per minute per square meter. The average oxygen consumption at various systemic flows and the relative contributions of hepatic arterial and portal venous blood are shown in Fig. 5.

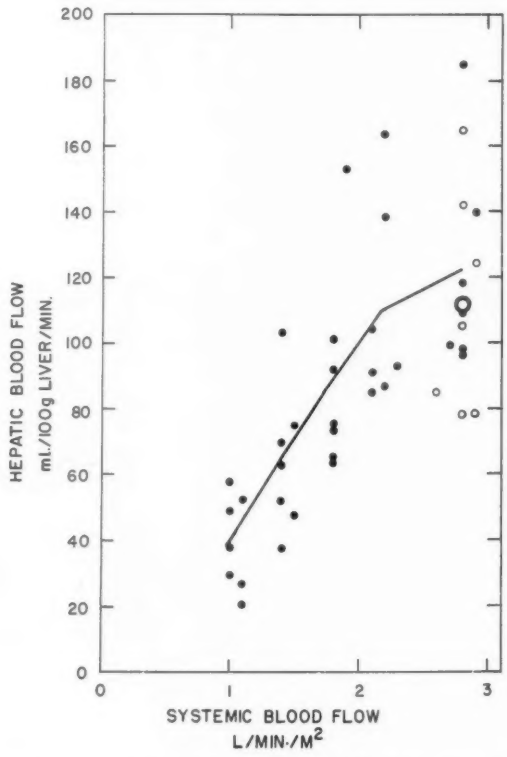

Fig. 3.—The relationship between hepatic blood flow and the animal's liver weight is shown at a normal controlled cardiac output and at various systemic flows. Open circles = control flows; solid circles = flow during cardiopulmonary bypass; double circles = mean control flow. The solid line is mean flow during cardiopulmonary bypass.

DISCUSSION

In order to evaluate properly the measurements of hepatic blood flow and oxygen consumption obtained during cardiopulmonary bypass, these values were obtained with the left ventricle maintaining a normal systemic flow as well as when systemic perfusion with nonpulsatile flow was by the pump-oxygenator. A flow of 2.8 L. per minute per square meter was accepted as a normal cardiac output for a dog under general anesthesia.[14] The other flow rates between 2.2 and 1.0 L. per minute per square meter were chosen since they represent those that are commonly employed clinically at various centers. Morphine, chloralose, and urethane were used for anesthesia since these agents are considered to provide a more physiologic preparation.

The determinations of total hepatic blood flow obtained during a period of controlled but normal cardiac output averaged 32.6 ml. per minute per kilogram. Although there have been several previous direct measurements of hepatic blood flow in the dog, most were carried out with some type of thermostromuhr, an instrument of questionable reliability.[5] Blalock and Mason[3] collected hepatic venous blood in unanesthetized dogs and the mean flow was found to be 28.6 c.c. per minute per kilogram. MacLeod and Pearce[9] determined a mean hepatic blood flow of 44 c.c. per minute per kilogram when hepatic venous blood was collected in dogs anesthetized with ether. Selkurt[12] measured hepatic venous flow in 14 dogs anesthetized with pentobarbital and the average flow was essentially identical to that observed in the present study.

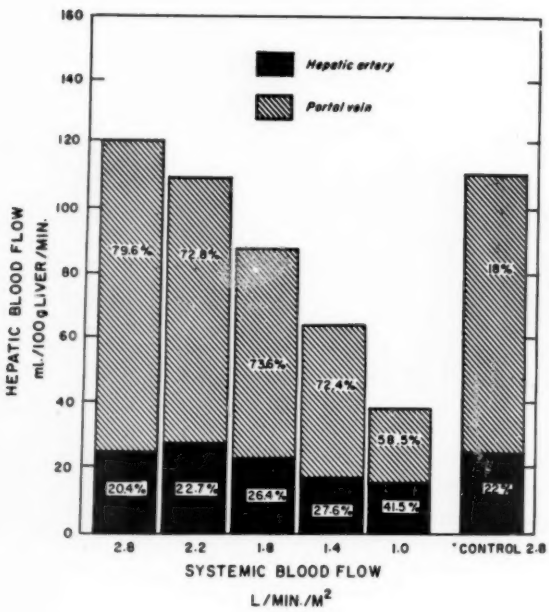

Fig. 4.

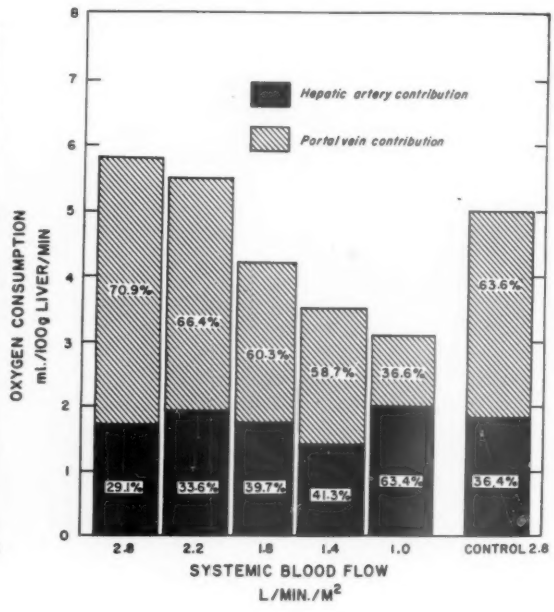

Fig. 5.

Fig. 4.—The relationship between hepatic artery and portal vein contribution to total liver blood flow at a normal controlled cardiac output and at various systemic flows during complete cardiopulmonary bypass.

Fig. 5.—The relationship between mean hepatic artery and portal vein contribution to liver oxygen consumption at a normal controlled cardiac output and at various systemic flows during complete cardiopulmonary bypass.

Hepatic blood flow during bypass at a perfusion rate of 2.8 ± 0.1 L. per minute per square meter was essentially equal to that in the control period. When the arterial flow rate was reduced to 2.2 ± 0.1 L. per minute per square meter hepatic blood flow decreased only slightly and proportionately less than when lower systemic flows were employed (Figs. 2 and 3). There was no correlation between this decrease in hepatic blood flow with the arterial blood pressure. In some animals aortic pressure remained constant as the systemic flow was reduced and in others it fell. Hamrick and Myers[6] have clearly shown a decrease in hepatic blood flow in dogs following bleeding. When the animals were subjected to a single hemorrhage amounting to 3.2 to 6.5 per cent of the

body weight, there was a good correlation between the amount of blood removed and the reduction in hepatic blood flow. No correlation was observed between the decline in arterial pressure and the decrease in hepatic blood flow.

In this study liver blood flow was 26.5 per cent of the systemic flow when the latter was normal. This value is in agreement with that obtained by Blalock and Levy[2] but slightly lower than that found by Werner and colleagues[16] who used an indirect method employing Bromsulphalein. During cardiopulmonary bypass, at various flow rates, there was little variation in this relationship.

Hepatic artery flow remained relatively constant at various systemic flow rates and most of the changes observed in hepatic venous flow were attributable to changes in portal flow (Fig. 4). The hepatic artery thus contributed 20.4 per cent of the total liver flow at a systemic flow of 2.8 ± 0.1 L. per minute per square meter but accounted for 41.5 per cent at an arterial flow of 1.0 ± 0.1 L. per minute per square meter. Hepatic artery flow was not significantly different when the left ventricle was maintaining a normal output or when the pump was delivering a similar flow. The measurement of hepatic artery flow may not include all arterial flow to the liver but the contribution of additional small arterial branches is apparently of no real significance.[7]

The oxygen consumption of the liver at a normal cardiac output averaged 5.0 ml. per 100 Gm. of liver. This was slightly higher than determined by Blalock and Mason[3] in unanesthetized dogs when a value of 4.2 ml. per 100 Gm. of liver per minute was obtained by measurement of the portal venous flow and hepatic artery flow by occlusion of the latter for a timed interval. During cardiopulmonary bypass at a flow of 2.8 ± 0.1 L. per minute per square meter, oxygen consumption of the liver was not significantly different (Fig. 5). At a flow rate of 2.2 ± 0.1 L. per minute per square meter the oxygen consumption still was well within the range of normal, and it was only after further reduction of the systemic flow that oxygen consumption fell. Of interest is the fact that the oxygen delivered by the hepatic artery to the liver parenchyma remained in general fairly constant but its proportional contribution rose from a value of 29.1 per cent at 2.8 ± 0.1 L. per minute per square meter to 63.4 per cent at a flow of 1.0 ± 0.1 L. per minute per square meter. Oxygen extraction from the portal blood decreases as portal flow decreases, as previously shown by McMichael.[10] This is due to decreasing difference in oxygen content between the portal vein and hepatic vein. However, the arteriovenous oxygen difference between hepatic arterial and venous blood increases, allowing for better oxygen extraction.

The splanchnic oxygen consumption with the heart pumping had a mean value of 6.7 ml. per minute per 100 Gm. of liver. Werner and associates[16] found it to be 7.9 ml. per minute per 100 Gm. of liver while Hamrick and Myers[6] and Blalock and Mason[3] determined a mean oxygen consumption of 4.5 ml. per minute per 100 Gm. of liver. The splanchnic oxygen consumption during cardiopulmonary bypass rose to 8 ml. per minute per 100 Gm. of liver and remained at this level until the systemic flow was below 2.2 ± 0.1 L. per minute per square meter. This is in agreement with Werner and co-workers who found that a blood loss of 1 per cent of body weight did not influence

splanchnic oxygen consumption. Hamrick and Myers showed no significant reduction in splanchnic oxygen consumption after a blood loss of 6.5 per cent of body weight of the dog. Only if further and sustained shock was induced did a reduction in splanchnic oxygen consumption occur.

Splanchnic oxygen consumption in this study did not markedly change until a systemic flow of 1.4 ± 0.1 L. per minute per square meter was reached, but hepatic oxygen consumption at this flow was greatly reduced. At 1.8 ± 0.1 L. per minute per square meter the splanchnic oxygen consumption was reduced by 13.0 per cent, but the liver oxygen consumption had been reduced by 28.0 per cent. This indicates that the liver is more vulnerable to reduced flows than the studies on splanchnic oxygen consumption done by Hamrick and Myers would indicate.

SUMMARY

The various components of hepatic blood flow were measured in normal dogs during cardiopulmonary bypass at systemic flows ranging from 2.8 to 1.0 L. per minute per square meter. Total hepatic flow was reduced at perfusion rates less than 2.2 L. per minute per square meter as was the oxygen consumption of the liver. Hepatic artery flow remained relatively constant at all perfusion rates and the decreases in total flow and oxygenation were attributable to reduced portal venous flow. It is concluded that a normal blood flow to the liver and normal oxygenation of its parenchyma can be maintained during cardiopulmonary bypass at a flow of 2.2 L. per minute per square meter.

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HEMODYNAMICS AND METABOLISM OF INDIVIDUAL ORGANS DURING EXTRACORPOREAL CIRCULATION

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THE increasing role of extracorporeal circulation in surgery has necessitated more detailed analysis of its effects upon individual organs to facilitate the interpretation of certain complications. A variety of factors has been mentioned in the etiology of these disorders, including hypoxia, abnormally elevated blood oxygen tension, and emboli of bubbles, fibrin, or silicone.[1, 3, 4, 5, 7, 8, 10-14, 17, 18] The lack of data on blood flow distribution and metabolism in various regions of the body has hampered complete evaluation of such sequelae, and the present studies were undertaken to investigate the effects of extracorporeal circulation on blood flow, vascular resistance, and oxygen consumption in the brain, kidney, intestine, and extremity.

MATERIALS AND METHODS

Studies on 58 mongrel dogs, weighing from 9 to 15 Kg., form the basis of this report. All animals were anesthetized with Nembutal (30 mg. per kilogram administered intravenously) and were operated upon under sterile technique. Extracorporeal circulation was performed with a Sigmamotor pump and bubble oxygenator, using 100 per cent oxygen, for periods ranging from 15 to 45 minutes. Cannulation was performed in standard manner. Femoral arterial blood pressure was monitored continuously with a strain gauge. Venous and spinal fluid pressures were measured with capillary monometers, and oxygen contents of arterial and venous blood were obtained by the technique of Scholander and Roughton.[16]

The preparations for the study of flow through the brain, kidney, intestine, and extremity have been reported previously in detail.[6, 9, 15] Cerebral flow was measured by shunting the arterial blood flow to the brain through a constantly recording magnetic rotameter. Renal, intestinal, and extremity flows were measured intermittently, by utilizing the venous outflow technique, whereby the venous flow from the renal, superior mesenteric, or femoral veins was returned through a plastic Y tube, permitting intermittent sampling from the sidearm (Fig. 1).

Two determinations were generally recorded for each of 4 periods: (1) initial control, (2) high flow perfusion (in excess of 50 c.c. per kilogram per

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minute), (3) low flow perfusion (less than 50 c.c. per kilogram per minute), and (4) final control. Pressure recordings, flow determinations, and simultaneous oxygen samples for these periods were analyzed for this report.

Blood flow was converted to cubic centimeters per 100 Gm. of wet tissue per minute. The intestinal calculations were based on the weight of the intestinal tube in the superior mesenteric distribution, and the extremity calculations on the weight of the leg, including bone, below the femoral catheter. Vascular resistance was calculated as the dividend of mean arterial pressure (millimeters of mercury) and flow (cubic centimeters per 100 Gm. per minute). Oxygen consumption was derived as the product of arteriovenous oxygen difference (volume-per cent) and flow (cubic centimeters per 100 Gm. per minute).

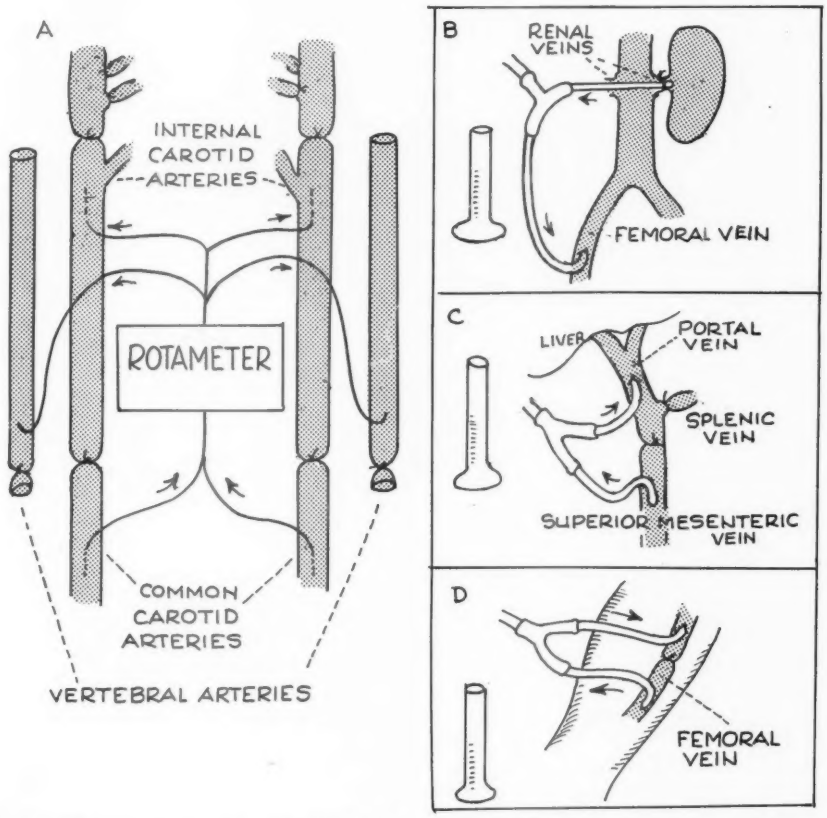

Fig. 1.—Diagrams of the methods used for the measurement of blood flow through individual organs. *A*, Cerebral flow was monitored with a magnetic rotameter. Blood was shunted from the common carotid arteries, through the rotameter, and returned to the internal carotid and vertebral arteries. *B*, *C*, and *D*, Renal, mesenteric, and femoral flows were measured by intermittently sampling the venous return from the sidearm of the Y tubes, after completion of the cannulations.

Temperature was maintained with circulating water blankets or electric heating pads and was monitored with a telethermometer. In the cerebral preparation a thermistor probe was inserted into the rectus abdominus muscle. In the experiments involving renal, mesenteric, and femoral flow, temperatures were recorded with probes inserted directly into the respective organs.

RESULTS

Blood Flow (Fig. 2).—Cerebral flow in 18 animals was found to be directly proportional to the mean systemic blood pressure both with and without extracorporeal circulation. This exact relationship was maintained at all levels, and very small alterations of pressure were immediately reflected in a corresponding alteration of flow as recorded by the rotameter. Cerebral flow changed little during extracorporeal circulation, except in the low flow perfusion group in which the mean systemic pressure was also reduced.

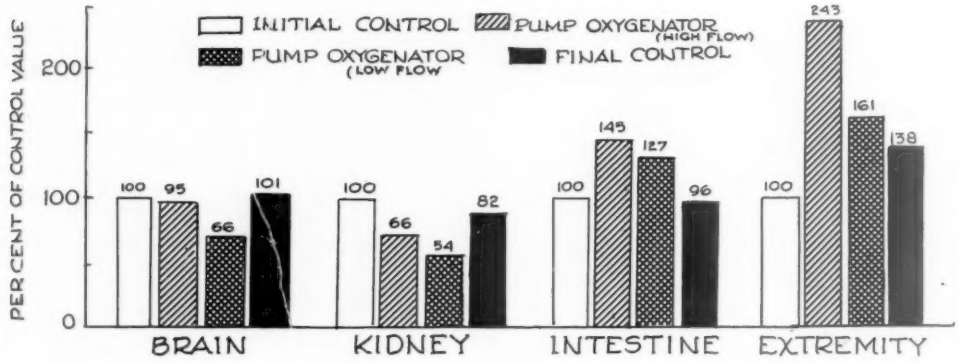

Fig. 2.—The effect of extracorporeal circulation on blood flow through individual organs. Cerebral flow remained relatively constant, renal flow decreased, and intestinal and extremity flows increased.

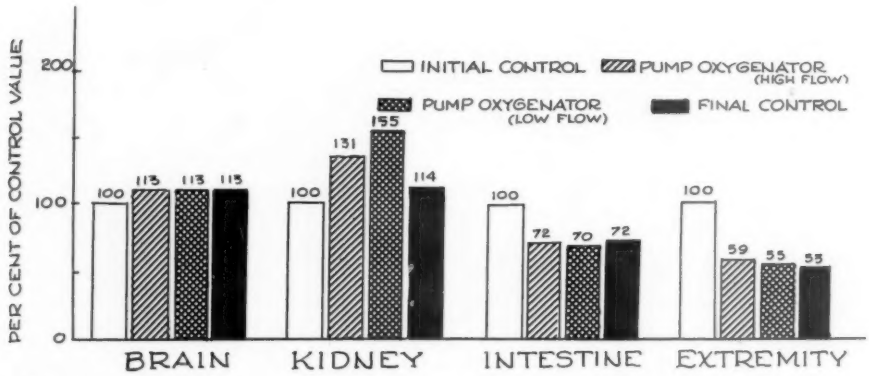

Fig. 3.—The effect of extracorporeal circulation on vascular resistance in individual vascular beds. Cerebral resistance changed little, renal resistance increased, intestinal and extremity resistances decreased.

Renal, mesenteric, and femoral blood flow, in 9 animals each, exhibited a much wider and less predictable pattern in relation to the blood pressure. Mean renal flow during perfusion, moreover, decreased from control values without corresponding pressure reduction. Mean mesenteric and femoral flow rates during extracorporeal circulation showed an increase over previous control values.

Extracorporeal circulation values for cerebral flow, renal flow, and femoral flow tended to persist into the final control period, but those for mesenteric flow reverted to the initial control value.

Vascular Resistance (Fig. 3).—Cerebral vascular resistance showed little change, although a slight mean increase of 13 per cent occurred during extracorporeal circulation and persisted into the final control period. Renal resistance showed a mean increase of 31 and 55 per cent, respectively, for high flow and low flow perfusion, respectively. Mesenteric resistance decreased to 71 per cent of control values during perfusion, and extremity resistance dropped to 57 per cent of controls. The values of resistance in each case tended to persist into the final control periods.

Oxygen Consumption (Fig. 4).—Cerebral oxygen consumption during extracorporeal circulation dropped to 55 per cent of control values for both high and low flow groups, and this decrease persisted into the final control period. Renal and extremity oxygen consumption increased somewhat during extracorporeal circulation. Intestinal oxygen consumption decreased during perfusion. The decreases in oxygen consumption observed in the brain and intestine occurred without corresponding changes in blood flow and resulted from a narrowed arteriovenous oxygen difference, due to increased venous oxygen content. Renal oxygen consumption increased slightly as a result of a widened arteriovenous difference, although flow dropped markedly. Extremity oxygen consumption remained approximately the same during extracorporeal circulation in spite of the marked increase in flow.

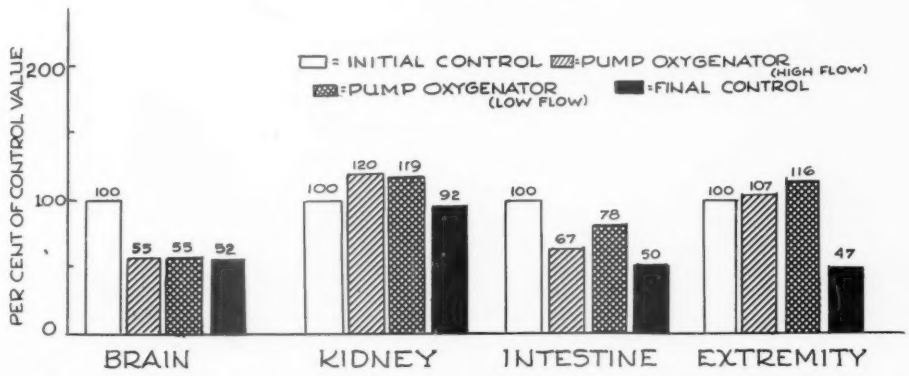

Fig. 4.—The effect of extracorporeal circulation on oxygen consumption in individual organs. Cerebral and intestinal oxygen consumption decreased, renal consumption increased slightly, and extremity consumption remained constant.

Venous and Spinal Fluid Pressure.—Central venous pressures monitored in the inferior and superior venae cavae in 10 animals showed only slight changes during extracorporeal circulation, except for several animals with malfunctioning venous outflow catheters which exhibited marked increases in superior vena caval pressure. Venous pressures of the mesentery and extremity showed a slight increase during extracorporeal circulation and the venous pressure of the kidney remained unchanged.

Spinal fluid pressure was closely correlated with superior vena caval pressure, and also showed marked elevation in the animals with inadequate venous outflow during perfusion.

Response to Vasopressor (Fig. 5).—In four experiments of each group a vasopressor substance (l-norepinephrine) was administered. This resulted in a marked increase in mean blood pressure in all experiments. Cerebral blood flow increased very strikingly in linear fashion with this increase in systemic blood pressure; an average increase of 250 per cent was observed. Mesenteric, renal, and extremity blood flow all decreased markedly; the maximum decrease in flow was observed in the extremity. In terms of vascular resistance it was noted that, while cerebral vascular resistance remained approximately the same, renal vascular resistance increased 565 per cent, mesenteric vascular resistance increased 660 per cent, and the vascular resistance of the extremity in these experiments increased to infinity as a result of the complete cessation of venous return.

DISCUSSION

Hemodynamic evaluation of organs involves consideration of the interrelationship of pressure, flow, and vascular resistance. Total body values for these variables and for oxygen consumption represent the net result of individual changes in different vascular beds and organs.

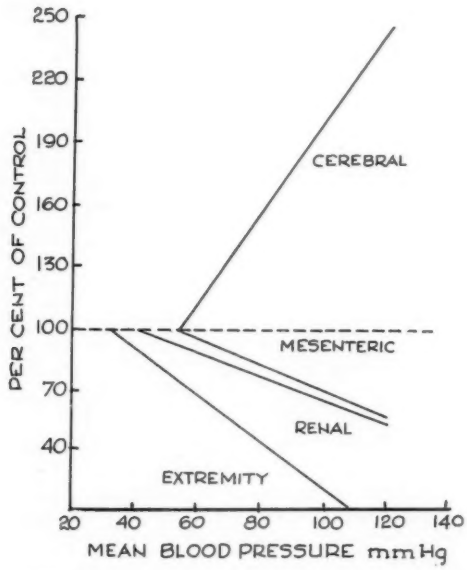

Fig. 5.—The effect of l-norepinephrine on organ blood flow during extracorporeal circulation. Cerebral flow increased markedly, and corresponding decreases in flow were observed in the other regions studied.

Cerebral blood flow was essentially dependent on the arterial blood pressure, due to the relatively passive role of cerebral vascular resistance under most conditions. This relationship has been recognized previously and its application to extracorporeal circulation was suspected prior to confirmation by direct measurement.

The greater role of resistance in determining flow through other vascular beds is evident from the less predictable flow rates through kidney, intestine, and extremity, both with and without extracorporeal circulation. Furthermore,

an individual response of vascular beds to perfusion was demonstrated, since cerebral resistance remained almost unchanged, renal resistance increased significantly, and mesenteric and extremity resistance decreased.

The unreliability of perfusion rates as indicators of organ flow was also evident from these data, since pressure was the primary determinant of cerebral flow, whereas resistance played an important role in determining flow in other organs.

Oxygen consumption data also demonstrated individual organ variability, with no uniform relationship to pressure, flow, or vascular resistance. Cerebral and intestinal oxygen consumption during perfusion decreased from previous control values, although cerebral flow showed only slight variation and mesenteric flow actually increased. Renal oxygen consumption increased slightly in spite of decreased flow, and extremity oxygen consumption remained constant with increased flow. The decreased cerebral and intestinal oxygen consumption resulted from increased venous oxygen content and could not be correlated with changes in temperature or pH.

The pathogenicity of this altered cerebral metabolism has not been defined, and the nature of our preparation precluded survival experiments. No correlation was observed among decreased cerebral oxygen consumption, abnormal lactic or pyruvic acid metabolism, or increased brain volume. Nevertheless, the low values of cerebral[17] and total oxygen consumption[2, 5, 6, 9, 15, 16] observed with lower flow rates support the desirability for perfusion rates more nearly approaching normal cardiac output.

Striking increases in cerebral blood flow during perfusion were shown to follow the administration of l-norepinephrine. Since adequate cerebral flow is of paramount importance, it is apparent that judicious utilization of pressor agents may be helpful during or following cardiopulmonary bypass procedures. However, it should be noted that such increased cerebral flow was obtained at the expense of flow through other body regions, where marked increases in vascular resistance were found. One must therefore conclude that vasopressors, specifically l-norepinephrine, should be employed cautiously in extracorporeal circulation, and that careful correction of blood volume deficits should precede their introduction.

SUMMARY

1. Cerebral blood flow during extracorporeal circulation was essentially dependent on the systemic blood pressure, because of the passive role of cerebral vascular resistance.

2. Renal, intestinal, and extremity blood flow were not closely correlated with systemic pressure because of the greater role of vascular resistance.

3. The resistance in individual vascular beds was found to differ in response to perfusion. Cerebral resistance remained approximately unchanged, renal resistance increased, and intestinal and extremity resistance decreased.

4. Individual organ variability in oxygen consumption during perfusion was demonstrated. Cerebral and intestinal oxygen consumption decreased, renal oxygen consumption increased, and extremity oxygen consumption remained unchanged.

5. A vasopressor agent (l-norepinephrine) administered during extracorporeal circulation produced striking increase in cerebral flow, with correspondingly decreased flow through kidney, intestine, and extremity.

6. No change in cerebral resistance was produced by l-norepinephrine but great increases occurred in renal, intestinal, and extremity vascular resistance.

We are indebted to Mr. White H. Gibson and Mr. Patrick Hanley III, Tulane University School of Medicine, and to Dr. William H. Letson, Department of Surgery, Tulane University School of Medicine, for participation in a number of experiments included in this report.

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THE SUDOMOTOR TEST

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THE sudomotor test is a chloride excretion test devised to outline areas of decreased perspiration in the cutaneous distribution of lacerated or injured nerves. It is an adaptation of a filter-paper screening test for cystic fibrosis of the pancreas developed in the Department of Pathology of Hurley Hospital.[2] Filter paper impregnated with silver chromate is moistened with chloride-free water and the chloride contained in sweat provides a handprint.

PRINCIPLE

Many subjective tests have been used to evaluate nerve regeneration. Function of a hand cannot be evaluated completely by such tests as the pinprick, 2-point discrimination, cotton wool, and coin tests. All of these tests are helpful, but they are time consuming, difficult to perform accurately, and are sometimes misleading if the patient is disturbed by his injury. Recently a somewhat more lengthy nerve injury test has been described by Moberg.[4] This test makes use of the ninhydrin reaction with amino acids in perspiration; test papers must be heated for 5 to 10 minutes at 100° to 120° C. to develop the test pattern. The sudomotor test described here requires only a few minutes for its completion, is completely objective, and supplies instantaneous results for a lasting record.

Perspiration results from stimulation of sweat glands by sympathetic fibers carried in peripheral nerves.[5] It is upon this principle that the sudomotor test is based. Many investigators have carried out exhaustive studies to establish innervation of the sweat glands. Goltz,[3] in 1875, first found that stimulation of the distal end of the divided sciatic nerve in a young kitten produced sweat in the foot pad. Langley concluded that the sudorific fibers of sweat glands in the cat are strictly sympathetic.[3, 5] The sympathetic supply for the hand arises from the first to the tenth thoracic roots and many surgeons and investigators operating upon human beings have shown that sympathetic denervation of the hand depends largely upon removal of the stellate and particularly the second thoracic ganglion through which these fibers pass. Only in the face are both sympathetic and parasympathetic sweat gland innervations found.[3] Sympathetic fibers travel via the anterior spinal roots to peripheral nerves.[5]

The chemical reaction of the sudomotor test is simple. Chloride is constantly excreted as insensible perspiration from the palms of the hands and soles of the feet. The amount of sweating is slightly increased by thermal stimuli but is more readily affected by emotions.[5]

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The impregnated filter papers are similar to those described for the screening test for cystic fibrosis of the pancreas[2] except that the papers are larger and the chemical concentrations have been altered in order to provide a somewhat more sensitive reaction. The silver chromate reacts with the chloride in sweat to form a white precipitate, silver chloride. This is the indicator seen on the test papers as white handprints, with minute white specks in areas of perspiration and normal innervation. Regions with deranged sympathetic supply appear as clear areas or are lighter when contrasted with control prints from the other hand.

METHOD

Preparation of the test papers is not difficult. Fine grain No. 50 Whatman, 24 cm. in diameter, filter paper of high wet strength is dipped into 0.1 N silver nitrate, dried completely, then immersed in 0.2 N potassium chromate solution. These papers are then dried and are stored in the dark. Care should be taken that they do not contact substances containing chloride. Just prior to use they are moistened with chloride-free water; it is not necessary that the water is distilled.

Other test equipment which has proved of value includes two thumb forceps, a large shallow pan containing clean blotting paper, and a cylinder covered with foam rubber and Saran Wrap. The latter can be constructed from an adhesive tape carton. The steps in testing a patient are as follows:

1. The subject's hands should be washed 15 minutes prior to making the handprints.

2. Chloride-free water is poured onto the blotter in the shallow pan. The test paper is next placed in the pan and allowed to saturate evenly. An ordinary paint roller is useful for speeding saturation and smoothing the paper if any number of tests are to be performed.

3. The filter paper is then picked up with the forceps and placed on the testing cylinder. The curved surface afforded by the cylinder greatly facilitates taking prints from clawhands and uneven surfaces. A smaller cylinder may be constructed for use with children.

4. The subject's hand is pressed against the filter paper with the fingers held in a gripping fashion and the thumb lying along the opposite surface of the cylinder. Three to four seconds of contact is adequate, as all available chloride is rapidly precipitated. A control print should be made of the uninjured hand.

5. Papers are permitted to dry on a flat surface in the dark. They should be dated and labeled with a wax crayon on the back. A yellow crayon is also useful for outlining the handprints, particularly if there are extensive areas of denervation. Dried papers may be stored in a folder or envelope. Extensive exposure to light will cause the prints to turn black. If it is possible that the results may be needed later for medicolegal purposes, it is advisable to photograph the prints.

RESULTS

Various types of nerve injuries, both recent and old, have been tested in 21 individuals who varied in age from 3 to 60 years. Most of these patients were followed by private physicians who supplied much helpful material in this study; more detailed follow-up of some of these cases is planned for publication at a later date. All individuals were examined for function and sensation as well as trophic skin changes. The latter were characteristically seen following prolonged loss of perspiration. Drawings were made of the hands of many cases of nerve injury; prints were then made of both the injured and normal hands. The patients studied can be illustrated by three typical cases:

Brachial Plexus Injury.—The patient was a 17-year-old girl who had injured the left brachial plexus in an automobile accident 1 year previous to testing. Surgical exploration revealed an evulsion of nerve roots C_6, C_7, and C_8. Physical findings consisted of a complete absence of sensation of the arm, forearm, and hand, with marked wasting of all muscles and complete loss of function. Fig. 1 indicates the lack of perspiration in the paralyzed extremity as compared with the normal hand.

Fig. 1.—Brachial plexus injury. Injured hand on left; control on right.

Median Nerve Injury.—A 10-year-old schoolgirl had suffered a laceration of the distal end of the median nerve in the left palm 1 month previously. The distal branches to one-half of the thumb, index finger, and one-half of the middle finger on its lateral side were involved. Anesthesia was found in these areas and on the thenar eminence and radial side of the palm. Arrest of perspiration accurately follows the pattern of the lacerated nerve (Fig. 2). This child exhibited a wrist drop when first seen, with associated diffuse atrophy of

the muscles of the forearm. Evidence of an intact radial nerve can be seen from the perspiration on the lateral half of the thumb. The physician's assumption that the wrist drop was probably on a psychoneurotic basis was thus confirmed and he has been able to restore the child's use of her forearm and wrist.

Fig. 2.—Median nerve injury. Injured hand on left; control on right.

Fig. 3.—Ulnar nerve injury. Injured hand on left; control on right.

Ulnar Nerve Injury.—A 32-year-old fireman was first tested 6 days after a laceration of the ulnar nerve in the left wrist. Because of a plaster mold, only the fingers could be tested at this time. Anesthesia was present in the ulnar innervation and decreased perspiration was seen, as indicated by lighter

prints on one-half of the ring finger and all of the fifth finger. At 6 weeks, slight clawing had developed, with interosseous and hypothenar wasting. A repeat print (Fig. 3) showed no sweating in the ulnar nerve distribution. Subsequently the patient was re-explored and inadequate approximation of the nerve ends was found. The re-anastomosis was performed and the patient is being followed at the present time.

From the cases observed, it has been found that the area of absent sweating closely matches that of anesthesia and functional loss. Tests done on patients shortly after injury suggest that this phenomenon occurs promptly. Patchy areas of hyperhidrosis have been found along the borders of recovery. Retesting of patients at 2- to 4-week intervals has generally been sufficient to follow the progress of their recovery.

SUMMARY

A chloride precipitation screening test for cystic fibrosis of the pancreas has been modified for evaluation and clinical follow-up of peripheral nerve injuries. It is based on the absence of perspiration from sweat glands in the distribution of lacerated peripheral nerves. Regenerating nerves show a concomitant recovery of the sweat pattern in the areas of their distribution. This sudomotor test is therefore a valuable prognostic procedure. It should prove useful in detecting psychoneurotics and malingerers and may aid the surgeon in avoiding malpractice suits. The test is of particular value in preoperative evaluation of nerve injuries which require difficult decisions for reoperation and resuturing.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

VENOUS AND ARTERIAL CONTRAST RADIOGRAPHY IN STILLBORN FETUSES

IMPLICATIONS IN NEONATAL RESUSCITATION

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IN PERFUSION experiments in which previable premature human fetuses have been used, it has been noted on numerous occasions that an injection of oxygenated blood via an umbilical artery has revived a failing heart after a similar injection via the umbilical vein had been without benefit. Intravenous transfusions were effective as long as cardiac contractions were of sufficient vigor to maintain blood pressure but were disappointingly ineffective after blood pressures had fallen to low levels. Recently an intra-arterial transfusion of 150 ml. of oxygenated blood successfully restarted the heart of a cooled, asphyxiated newborn infant which stopped after 76 minutes of apnea.[14, 15] That intra-arterial transfusions can revive hearts when transfusions by the usual route are no longer of benefit is of importance, and requires an explanation for its comprehension. In this report the rationale for the use of intra-arterial transfusions is discussed briefly. Then in the data section are presented the results of injections of radiopaque substances in stillborn fetuses via the intravenous and intra-arterial routes.

RATIONALE FOR INTRA-ARTERIAL TRANSFUSIONS FOR THE FAILING HEART

In the first place it must be emphasized that no blood introduced into the circulatory system via the usual intravenous route can reach the coronary arteries until after it has made a complete circuit of the pulmonary system, passed through the left atrium and been pumped into the ascending aorta by the left ventricle. In addition, adequate coronary circulation can occur only when the left ventricle is pumping against a considerable head of pressure. The myocardium of the failing heart at first lacks adequate contractile power to

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maintain this pressure and then, as conditions deteriorate further, becomes incapable of moving the blood at all, even though feeble contractions may continue for a period. Intravenous transfusions at this stage would hardly be expected to influence the outcome favorably.

In addition, as illustrated in Fig. 1, increasing venous return to a flabby, failing heart may actually accelerate the rate of deterioration. Blood delivered to such a heart by either the superior or inferior vena cava will cause distention of first the right atrium and then, passing through the right atrioventricular valve, the right ventricle. Because of the inelastic nature of the pericardium this distention will produce compression of the myocardium and particularly of the veins which drain it. (The coronary arteries would not be expected to be affected because of their thick elastic walls.) The anterior cardiac veins draining the right atrium, the small cardiac vein draining the right ventricle, and the coronary sinus would all be compressed. In addition, their smaller tributaries might be completely occluded. It is probable also that both the great cardiac vein and the middle cardiac vein would be constricted and many of their smaller tributaries completely closed. These mechanical factors are probably responsible for the improvement in heart action noted by Bigelow and associates[1] and others in hypothermic dogs when intravenous pressures are reduced by venous bleeding.

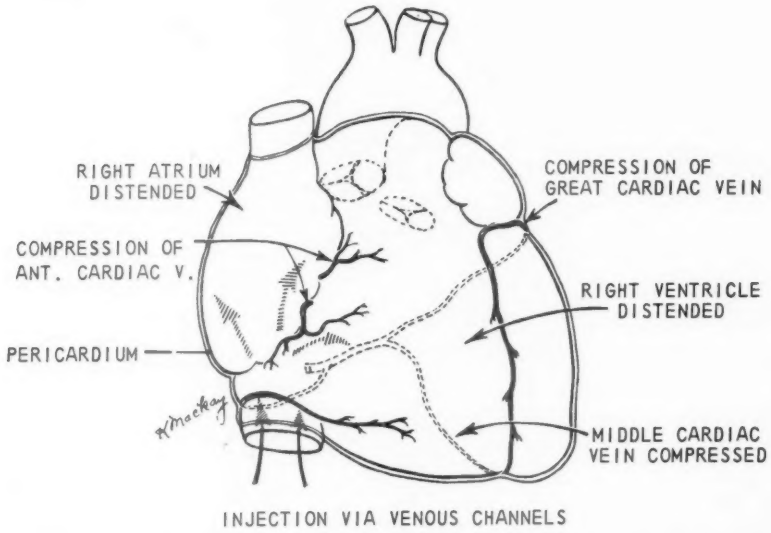


Fig. 1.—Results of intravenous transfusion into a flabby atonic heart. Injected blood dilates right atrium and right ventricle, filling pericardial cavity, reduces coronary flow by compressing all coronary vessels, particularly the veins.

The net result, therefore, of increasing the venous return to the failing heart would be to reduce coronary flow by constricting the veins and thereby increase the severity of the oxygen lack of the myocardium without in any way combatting the stasis in the coronary arteries.

Fig. 2 illustrates the result when a retrograde injection is made into a branch of the systemic aorta. The aortic valves retain their competence even after death as may be demonstrated in fresh unembalmed human or beef hearts.

Since the walls of the arteries are sufficiently strong to resist distention and there are no organs such as the liver which can accommodate large additional quantities of blood, very little volume is needed to cause the movement of blood through the vital vascular beds such as those supplying the heart and brain. In our experiments with unembalmed stillborn fetuses it was found that as little as 2 ml. of radiopaque solution injected into an umbilical artery reached the aortic valves, whereas it required more than 60 ml. injected into the umbilical vein to reach the right side of the heart.

If the transfusion is accompanied by pulsations in pressure of the same order of magnitude as occur under normal cardiac contractions, normal filling of the coronary arteries may be expected. In Fig. 2 is illustrated the dilation of the aortic bulb and of the left and right coronary arteries that would take place during such a pressure pulse. As the oxygenated blood reaches the myocardium more vigorous contractions are possible. With the improvement in pumping efficiency of the left ventricle coronary flow improves with each contraction and, provided there has been no permanent damage, further assistance may be unnecessary. Retrograde injection of blood will actually increase the effectiveness of the first few pumping contractions by elevating the pressure and thus forcing a larger proportion of the stroke volume into the coronaries.

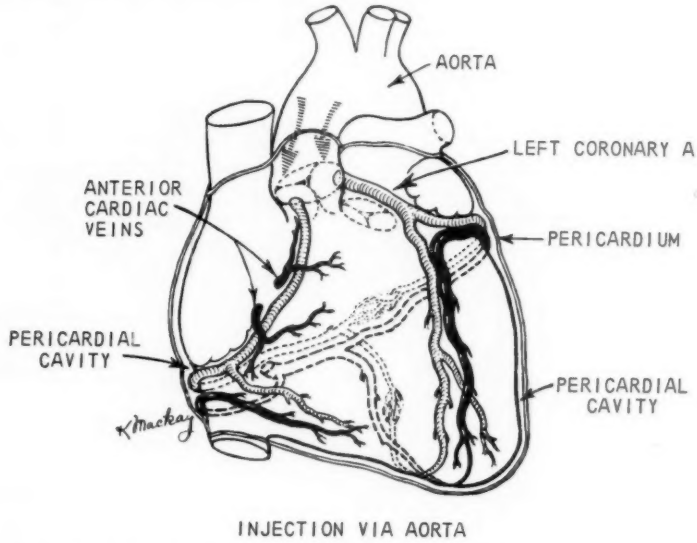


Fig. 2.—Results of intra-arterial transfusion into a flabby atonic heart. Injection enters left and right coronary arteries, provides fresh blood for myocardium.

This picture is somewhat more complex in the premature and neonatal infant because of the vascular bypass through foramen ovale and ductus arteriosus. The extent to which these shunts alter the course of injected fluids can be seen in the x-rays which follow.

This deductive analysis provided a rationale for the observed results on perfused premature fetuses. It also suggested some methods of testing the hypothesized mechanism. It did not, however, prepare us for the findings when unembalmed stillborn fetuses were transfused with radiopaque solutions through an umbilical vein.

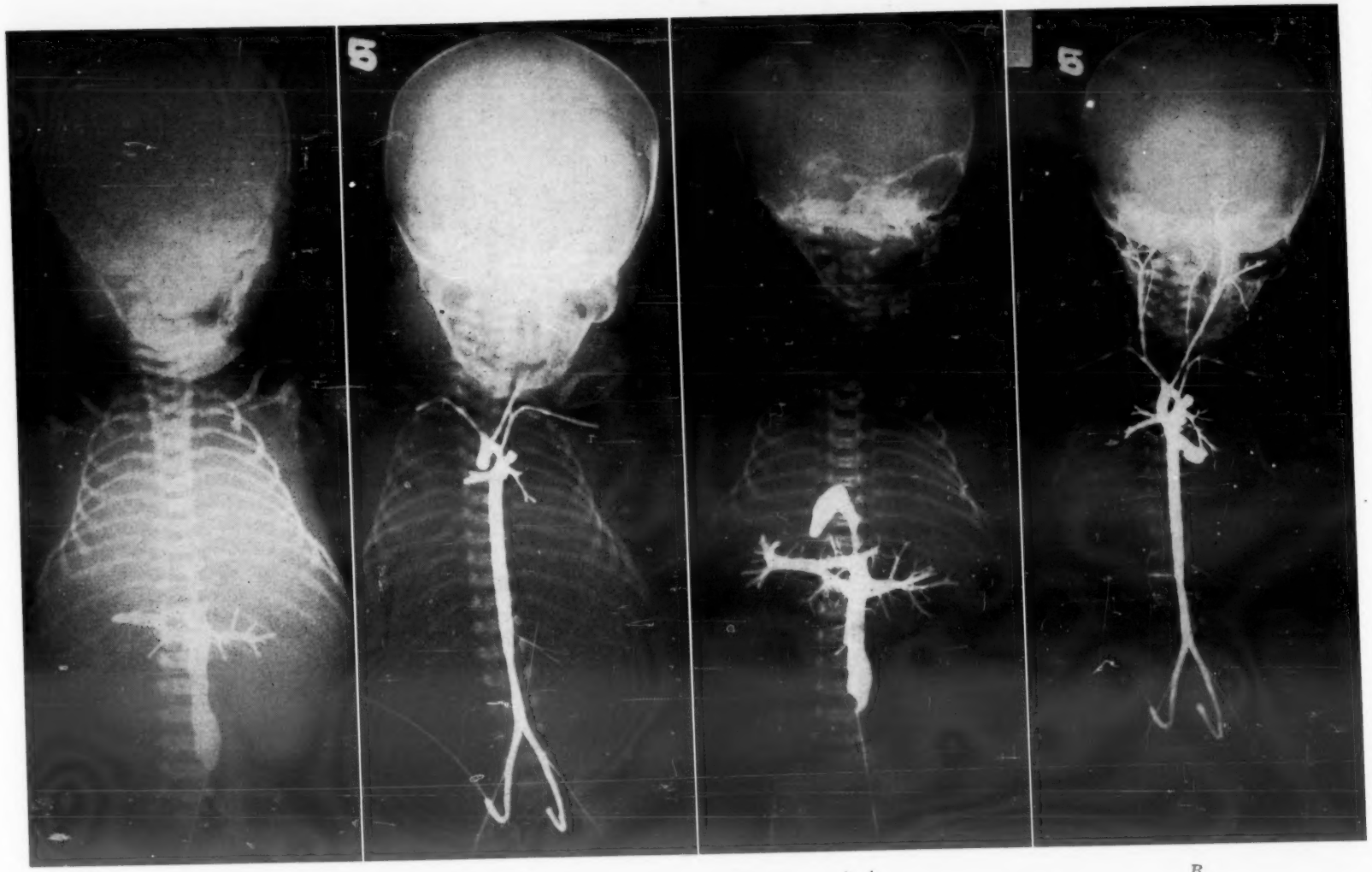
INJECTIONS OF UNEMBALMED STILLBORN FETUSES WITH RADIOPAQUE SOLUTIONS

Unembalmed stillborn fetuses were injected with radiopaque substances and the paths of the injected materials were recorded by x-ray. Since hydrodynamically a flabby atonic heart differs but slightly from one that has stopped completely, these records were used as an indication of the course of injected blood in a living though moribund newborn infant.

The first 5 infants were injected with water-soluble solutions. The radiographs of these infants which were taken during the later part of the injection period became progressively beclouded by the contrast medium which diffused through the walls of the smaller vessels. For subsequent injections oil-soluble contrast media were used. A more detailed analysis of the findings will be presented elsewhere; however, for this report two typical cases, one injected via the umbilical vein and the other via the right umbilical artery, are described and illustrated. Twenty 11 by 14 inch radiographs were taken of each baby after transfusion with a 50 per cent solution of n-propyl ester of 3:5 duodo-4-pyridone-N-acetic acid in peanut oil (Dionosil Oily). The pictures were taken after the following quantities were injected through an indwelling catheter: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 20, 25, 30, 35, 40, and 50 ml.

In general it may be said that the first 10 ml. of contrast medium introduced through the umbilical vein was largely contained within the liver and the portal system. At 10 ml. the inferior vena cava began to fill in a cephalocaudal direction, but even after 40 ml. none of the contrast medium had reached the aortic valves. On the other hand, rapid filling of the aorta and all its main branches occurred when the site of introduction was the umbilical artery. The right and left coronary arteries were visualized after only 4 ml. and the circle of Willis after only 7 ml. It appeared that the thick elastic walls of the arteries prevented the flooding of a single organ or group of organs during the injection such as occurred in the case of the intravenous injection.

The results of the injection of 2 and 4 ml. of the contrast medium are shown in Figs. 3 and 4, respectively. The baby with the intravenous injection is on the left, the one with the intra-arterial on the right. In Fig. 3, *A* the Dionosil is seen in the larger advehent hepatic veins and passing upward through the diaphragm toward the heart. Fig. 3, *B* was taken after the same volume had been injected intra-arterially. The contrast medium fills the entire aorta and has passed into the common iliacs, the subclavians, ductus arteriosus, and the proximal portions of the pulmonary arteries and left common carotid. Fig. 4, *A* shows further arborization of the hepatic veins, and the proximal part of the portal vein with the superior mesenteric and lienal veins recognizable. Above the diaphragm filling of the right atrium has started. Fig. 4, *B* presents a striking contrast. In it are seen all the major arteries as far as foramen magnum. Among the arteries which can be recognized in this picture are the external and internal carotids, vertebrals, internal mammaries, renals, superior mesenteric and arteries supplying the appendages, the brachial, and femoral. In addition, it will be noted that there has been reflux filling of the left ventricle through aortic valves which proved incompetent in this specimen. The most significant arteries from the point of view of this study, however, are the right



A. *B.*

Fig. 3.

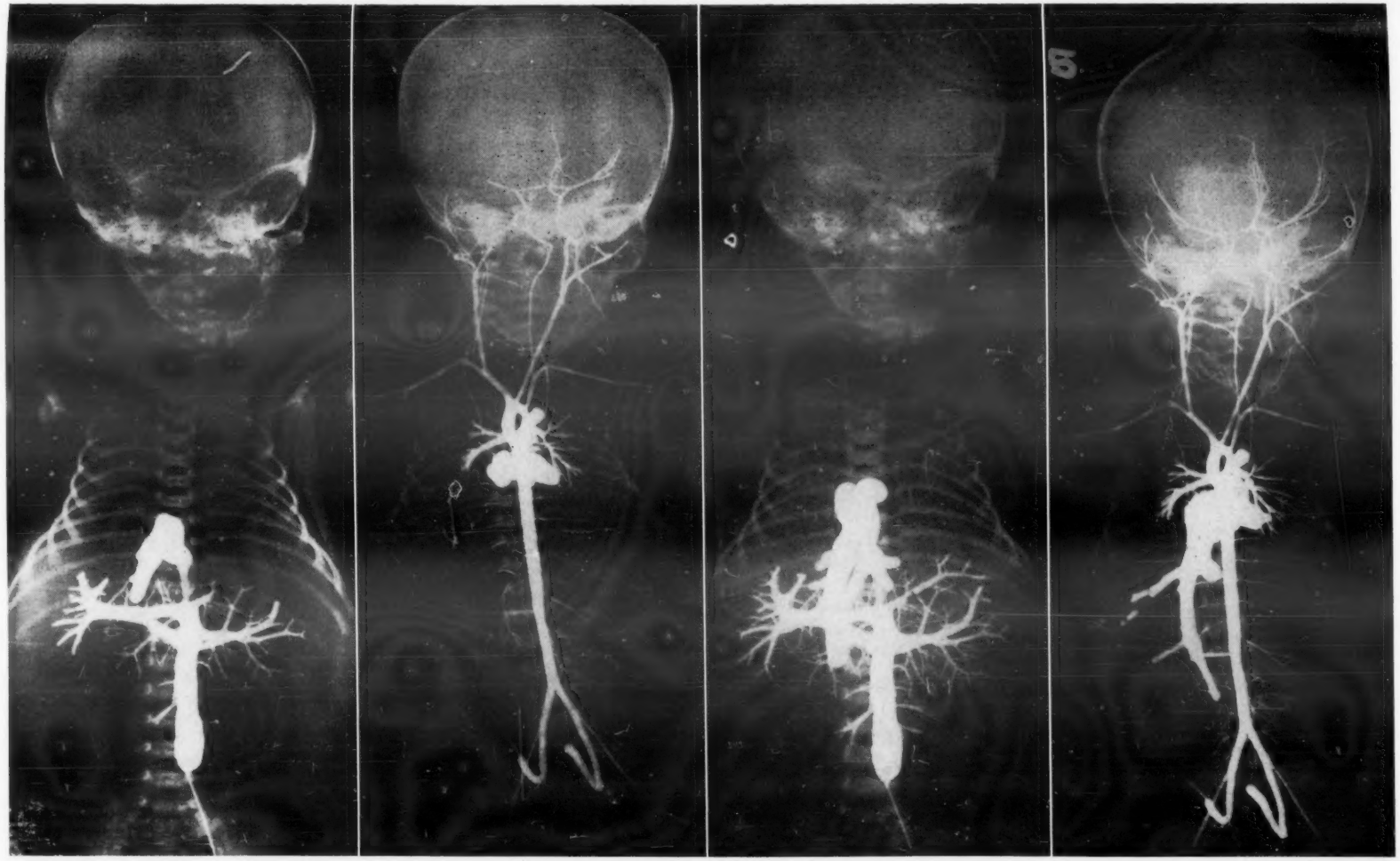
A. *B.*

Fig. 4.

Fig. 3.—Dionosil Oily (2 ml.) injected intravenously (*A*) and intra-arterially (*B*). *A*, Umbilical and advehent hepatic veins seen. *B*, Arteries filled include: entire length of aorta, common iliacs, subclavians, left renal, ductus arteriosus, and pulmonaries.

Fig. 4.—Dionosil Oily (4 ml.) injected intravenously (*A*) and intra-arterially (*B*). *A*, Structures seen include: hepatic veins, right atrium, and proximal parts of portal, superior mesenteric, and lienal veins. *B* (Intra-arterial), Arteries seen, in addition to those in Fig. 3 *B*, include: left and right coronary, vertebral, external and internal carotid, internal mammary, axillary, coeliac, and superior mesenteric.

atrium, and proxinal parts of portal, superior mesenteric, and
3 *B*, include: left and right coronary, vertebral, external and internal carotid, internal mammary,



A. *B.*

Fig. 5.

A. *B.*

Fig. 6.

Fig. 5.—Dionosil Oily (6 ml.) injected intravenously (*A*) and intra-arterially (*B*). *A*, Structures seen, in addition to those seen in Fig. 4, *A*, include: revehent hepatic veins and inferior vena cava. *B*, Arteries seen, in addition to those in Fig. 4, *B*, include: basilar artery, additional branches of internal carotid and external carotid arteries, left and right atria.

Fig. 6.—Dionosil Oily (10 ml.) injected intravenously (*A*) and intra-arterially (*B*). *A*, Filling of left atrium through foramen ovale. of inferior vena cava to L_1 and further elaboration of the hepatic veins is seen. *B*, Attention is called to the circle of Willis, anterior and middle cerebral, middle meningeal arteries, and inferior vena cava which is filled to L_3.

A. *B.*

Fig. 7.

A. *B.*

Fig. 8.

Fig. 7.—Dionosil Oily (20 ml.) injected intravenously (*A*) and intra-arterially (*B*). *A*, The innominate, right internal jugular veins, and transverse sinus have filled. More medium has entered the left atrium, and the inferior vena cava has filled to L4. *B*, All major arteries have filled and, in addition, the inferior vena cava and proximal part of the superior vena cava.

Fig. 8.—Dionosil Oily (35 ml.) injected intravenously (*A*) and intra-arterially (*B*). *A*, Further elaboration of the venous pattern with dilatation of the major vessels is seen. Filling of superior sagittal sinus, left transverse sinus, and basilar plexus has begun. *B*, Filling of the venous channels has progressed as far superiorly as in *A* and farther inferiorly. Note lack of distention of veins in *B*.

and left coronaries indicated on the illustration by arrows. This very early filling of the coronary arteries appears to be the explanation for the efficacy of intra-arterial transfusions for the flagging or moribund heart which had been noted earlier.[3, 15]

Fig. 5, *A* illustrates the result of injecting 6 ml. of contrast through the umbilical vein. Further filling of the hepatic and portal system may be seen, and the inferior vena cava is beginning to appear. The corresponding film of the intra-arterial series, Fig. 5, *B*, shows further elaboration of all the arterial systems, and especially of those in the head. In the heart region the injection mass has reached the right atrium. The beginning of reflux filling of the inferior vena cava is forecast by the swelling at the caudal part of the atrial shadow.

The radiographs in Fig. 6 were taken after 10 ml. had been injected. In Fig. 6, *A* it is seen that although there is further filling of the inferior vena cava most of the injection mass is still limited to the hepatic and portal systems. In the heart passage through foramen ovale with consequent filling of the left atrium has begun. The greatest change between Fig. 5, *B* and 6, *B* is the filling of the inferior vena cava as far as L_3 and the beginning of filling of the portal vein. However, in the leg the anterior tibial, posterior tibial, and peroneal arteries are now visible and the arterial supply of the brain and brain stem is becoming increasingly clear.

The radiographs shown in Fig. 7 were made after 20 ml. of contrast medium had been injected. In 7, *A* is seen an increase in the complexity of the venous pattern in the upper abdomen, but most of the additional contrast medium has entered the heart and the superior vena cava. On the right side the internal jugular vein and transverse sinus is filled. On the left the innominate and the beginning of the vertebral vein has filled. Fig. 7, *B* on the other hand shows further elaboration of both the arterial and the venous pattern as compared with Fig. 6, *B*. Most of the 10 ml. which was injected after Fig. 6, *B* was taken has entered venous channels. Filling of the inferior vena cava is complete and the iliac veins are partially filled. In the upper abdomen the umbilical vein, ductus venosus, and main branches of the portal system can be recognized. In the thorax the superior vena cava has filled and the innominates are beginning to fill. Further filling of arteries is to be noted particularly in the head with filling of the intracranial vessels being especially obvious. Further elaboration of the vascular patterns of the extremities permits the recognition of most of the named branches. However, the most interesting new development at this stage is the appearance of the contrast medium in the marrow cavities of the femurs, tibias, and the left humerus.

Fifteen milliliters were injected between Figs. 7 and 8. As illustrated in Fig. 8, *A* there was still further filling of the hepatic and portal venous channels, inferior vena cava, heart, and structures draining into the superior vena cava. Within the calvarium the right cavernous and transverse sinuses are filled and the injection mass has reached the superior sagittal sinus and left transverse sinus. On the left there has been further filling of the vertebral vein and internal vertebral plexus.

Fig. 8, *B* shows that after an intra-arterial injection totaling 35 ml. the arterial pattern for the entire body was virtually complete. In addition, the major venous channels were partly filled. As was noted when the venous route was employed, the liver and portal system accommodate considerable quantities of fluid. However, in the case of the liver, the pattern of filling differs with the two injection procedures. In Fig. 8, *B*, because the filling is chiefly from above, the revehent vessels—the left and right hepatic veins—fill first and are the most prominent, whereas in Fig. 8, *A* the advehent vessels are equally large and well arborized. Superiorly filling of the venous channels of Fig. 8, *B* resembles rather closely that seen in Fig. 8, *A* with the exception that less venous dilatation is seen. The constriction of the internal jugular veins at the level of the clavicle shown in Fig. 8, *A* is seen in Fig 8, *B* to be at the point where they are crossed by the subclavian arteries. In Fig. 8, *B* in addition the innominate vein is seen to be constricted where it is crossed by the innominate and left common carotid arteries. There is no filling of the veins of the extremities in either specimen.

In summary, these x-ray studies of stillborn babies showed consistent differences in the pathways taken by a nonmiscible contrast medium. When injected intra-arterially only small volumes (4 ml. in the case illustrated) were required to fill the arteries supplying the heart (the coronaries) and the respiratory centers of the medulla (the vertebrals and basilar artery). Early filling of another pair of vital organs, the kidneys, was also seen (after only 2 ml.) when the route was intra-arterial.

Intravenous injections passed first to the liver, then to the portal system, right atrium, inferior vena cava, superior vena cava, and left atrium. Filling of the aorta did not take place until 50 to 60 ml. had been injected. These studies therefore provide a morphologic basis for our earlier findings that when the blood pressure has fallen to zero intravenous transfusions are ineffective, whereas intra-arterial transfusions may successfully resuscitate a heart even after cardiac arrest.

DISCUSSION

The vessels within the umbilical cord provide a very convenient route by which transfusions may be given and transfusions of oxygenated blood have proved beneficial for the asphyxiated newborn infant.[14, 15] In cases in which heart action is strong enough to maintain some blood pressure, the intravenous route is entirely satisfactory. However, intra-arterial injections appear to be necessary if the blood pressure is very low. The present studies offer an anatomic rationale for these observations.

The chief requirement for resuscitation from asphyxia is the delivery of oxygenated blood to the vital organs. Under ordinary circumstances this is only possible if the heart is contracting vigorously and for this adequate volumes of oxygenated blood must be delivered to the coronary arteries. This fact lends special significance to the early filling of the coronary arteries in the case of the baby injected intra-arterially. The patent intra-atrial foramen ovale of the newborn infant offers a short-cut, not present in the adult, by which an

intravenous injection can pass to the left side of the heart and thus reach the aorta without passing through the lungs. In spite of this fact, there was no filling of any part of the arterial tree until after 40 ml. had been introduced intravenously. Filling of the coronary sinus was recorded at 50 ml. and a shadow, questionably identified as the right coronary artery, was seen after 60 ml. had been injected. In striking contrast were the results when the injection was via an umbilical artery. One fifteenth of this volume (4 ml.) was sufficient for filling of both coronary arteries and only 7 ml. was required for complete filling of the circle of Willis. Thus, even with cardiac arrest, an intra-arterial transfusion of oxygenated blood may be expected to improve the oxygenation of the respiratory centers by the time the infant has received 10 ml. This finding appears to explain the onset of breathing only 3 minutes after the beginning of the transfusion in Case 4 of Westin, Miller, Nyberg, and Wedenberg.[14, 15] Since the heart was in arrest at the beginning of the period of transfusion, it is not likely that adequate oxygenation for firing by the respiratory centers could have been achieved in such a short time without direct perfusion of the medulla by the transfusion itself. This actually proved to be the situation in the adult dog in a series of experiments by Jones and co-workers[6] employing a standardized hypotension. They found that gasping which usually began within 5 seconds after the beginning of intra-arterial transfusion was prevented by clamping the vertebral arteries (which supply the medulla) but not the carotids (which supply the aortic receptors and provide the major supply for higher centers).

Intravenous transfusions date from the time of Richard Lower[9] (1665) and Jean Baptiste Denis[2] (1667). The first discussion of intra-arterial versus intravenous transfusion was that of Landois[8] in 1878, who concluded that the former was the route of choice. In 1883 Halsted[5] reported the successful use of a crude form of intra-arterial transfusion, called by him "refusion." Sixty years later Kohlstaedt and Page[7] (1943) revived interest in the intra-arterial route by reporting that 75 per cent of dogs recovered from an otherwise lethal hemorrhage if transfused intra-arterially while only 30 per cent recovered if the same volume of blood was returned by an intravenous route. Glasser and Page[4] (1948) demonstrated the value of intra-arterial transfusions for hemorrhagic shock. In 1950 Jones and colleagues,[6] using 35 per cent Diodrast at a pressure of 100 mm. Hg, found that very little entered the aorta when pressures were within the normal range (100 to 110 mm. Hg). When the dog's pressure was reduced to 70 mm. Hg, the injection reached the diaphragm. Below 50 mm. Hg they reported filling of all large branches of the aorta, including the coronary and vertebral arteries. Similar studies should be made upon newborn infants. Lacking these, the studies reported here show the same injection pattern for the stillborn fetus with no systemic pressure as Jones and his group found in living animals with less than 50 mm. Hg blood pressure. Their conclusions for the adult that intra-arterial injections are most effective when needed the most are in full agreement with those derived in this study for the newborn from a quite different approach.

In spite of its demonstrated benefits in adult dogs intra-arterial transfusion of oxygenated blood has not been used extensively because of the danger of gangrene resulting from subsequent arteriospasm at the injection site.[16] This contraindication is not present in the newborn infant which is provided with a pair of major aortic branches (the umbilicals) which are readily catheterized and whose subsequent constriction is part of the physiologic processes accompanying birth and does not interfere with the blood supply of any organ. Thus it appears that in addition to hypothermia[10-13] there is another important aid in reviving the moribund infant which has thus far been almost completely overlooked. The present study indicates the route by which intra-arterial transfusion might deliver oxygenated blood to the myocardium via the coronary arteries and to the respiratory center of the medulla by the branches of the basilar artery. It is probable that the latter is the explanation for the early onset of respiration observed in the babies reported earlier during the course of intra-arterial transfusions.[14]

The use of an immiscible contrast medium prevented the blurring of the pictures which occurs when the medium escapes into the tissues. Taking this into account, the pictures obtained on stillborn babies are remarkably similar to some of those of Lind and Wegelius[17, 18] which were made on living premature and full-term infants. Their studies also show an early filling of the liver in injections via the umbilical vein with retrograde filling of the inferior vena cava in an asphyxiated newborn infant (Fig. 14 in Lind and Wegelius[18]). Likewise, their intra-arterial radiographs show the same pattern of filling, including that of the coronary arteries, which was described here (Figs. 27 and 28 in Lind and Wegelius[17]). These findings lend added support to the rationale for the use of the intra-arterial rather than intravenous route which has been developed in this report.

SUMMARY

1. In a brief discussion of the rationale for intra-arterial transfusions, one factor not previously considered is emphasized. Intravenous transfusions by increasing the venous pressure will dilate the flabby atonic heart and compress the veins draining the heart wall. This may increase the oxygen deficiency of the myocardium and actually reduce the chances of recovery.

2. Human stillborn fetuses were injected with Dionosil Oily through the umbilical vein or an umbilical artery and were x-rayed after measured quantities had been introduced.

3. Most of the contrast medium was accommodated in the liver and portal system when transfused through the umbilical vein with filling of the cavae and heart taking place later. Filling of the aorta as a result of passage of the medium through foramen ovale and the left atrium and ventricle occurred much later.

4. Introduced through an umbilical artery, the contrast medium reached the kidneys and the aortic valves after only 2 ml. and filled the coronary arteries and major vessels of the head, as far as foramen magnum, after only 4 ml. All the major arteries in the body were visualized after 35 ml. had been introduced.

5. These injection studies provide an anatomic explanation for the earlier observations on living premature infants that, after intravenous transfusions were of no benefit, intra-arterial injections might reactivate effective pumping contractions by the heart.

We are grateful to Dr. Ted F. Leigh of Emory University Hospital for providing the facilities and the expert knowledge which made possible the excellent radiographs which we had for study. We are greatly indebted also to Mr. Joseph T. Jackson and the Department of Medical Illustration for reproductions of the radiographs which in some cases were better than the originals.

The senior author also wishes to acknowledge indebtedness to Dr. John Lind of the Wenner-Gren Cardiovascular Research Laboratory for providing facilities, assistance, and materials which made possible the studies of premature living humans during his stay in Stockholm.

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PERICARDIECTOMY FOR CHRONIC CARDIAC TAMPONADE IN CHILDREN

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THERE are numerous reports in the literature concerning pericardiectomy for chronic constrictive pericarditis and a few relating to pericardiectomy for tamponade due to chronic pericardial effusion. No paper has appeared in the literature, as far as we know, dealing specifically with these problems in children. For this reason we have felt it worthwhile to present 4 cases treated in this institution and to review the pertinent literature.

CASE REPORTS*

CASE 1.—The patient was first admitted on July 25, 1951, at the age of 15. The diagnosis of pulmonary tuberculosis had been made in January, 1950, and he had been treated in a sanitarium for 17 months. At the time of that admission he was said to have had ascites, hepatomegaly, dyspnea, and orthopnea. Digitalis treatment had not been appreciably beneficial. He was thought to have chronic constrictive pericarditis and was transferred to this hospital.

At this time he had some edema of the lower extremities and minimal ascites. The liver edge was palpable 8 cm. below the right mid-costal margin. The heart sounds were quiet, the blood pressure 95/90 mm. Hg, and the venous pressure 35 cm. H_2O. Fluoroscopic and roentgenographic studies revealed poor cardiac contractions, extensive pericardial calcification, and mild bilateral pleural effusion. Cardiac catheterization revealed high pressures in the venae cavae, right atrial pressure of 30/21 and a right ventricular pressure of 55/17 with a mid-diastolic plateau.

Pericardiectomy was performed on July 28, 1951. The pericardium was markedly thickened and calcified. It was removed anteriorly and posteriorly back beyond the mid-portion of the heart on both sides. Postoperatively the venous pressure fell to 26 cm. He lost 9 pounds within a few days.

When the patient was seen on October 22 he was obviously improved but not entirely well. There was still some ankle edema and his venous pressure was 24 cm. H_2O. He was, therefore, readmitted on March 17, 1952. Although he had felt much better he had occasionally required mercurial diuretics for mild peripheral edema and at times had noted dyspnea upon little exertion. On right heart catheterization the atrial pressure was found to be 18/11, and the ventricular pressure 60/13 with a mid-diastolic plateau. The femoral pressure was 110/67. The second operation was performed on March 22, 1952, through a left anterolateral thoracotomy. The remaining pericardium was excised back to the posterolateral border of the heart. The myocardium was thin and flabby. At the completion of the procedure his condition seemed precarious. The venous pressure had risen to 60 cm. H_2O and râles were audible in both lungs. Marked improvement followed the removal of 750 c.c. of blood. His convalescence was rapid and he was discharged on April 6, 1952.

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*Cases 1 and 2 have been mentioned in previous reports.[26, 27]

Examination of the excised pericardium on both occasions showed nonspecific fibrosis with calcification. There was nothing in either specimen to suggest tuberculosis.

He has remained entirely well and has led an actively normal life. When last examined his blood pressure was 130/70 mm. Hg, the venous pressure 10.5 cm. H_2O.

CASE 2.—The patient was a 16-year-old girl who was admitted on Aug. 16, 1955. She had been entirely well until 9 months previously when she fainted while dancing. Syncopal attacks after exercise occurred several times a week during the following 2 months. Seven months before admission she developed a low-grade fever, dyspnea, a feeling of fullness in her chest and neck, swelling of the face, hands, feet, legs, and abdomen. On admission to another hospital she was noted to be orthopneic and cyanotic, the heart sounds were distant and no murmurs were heard. The liver was enlarged. Roentgenograms revealed a markedly enlarged cardiac shadow. The electrocardiogram showed low voltage. First and second strength Mantoux tests were negative as was the histoplasmin skin test. It was apparent that she had cardiac tamponade and pericardiocenteses were performed on 3 successive days with the removal of over 2 L. of fluid. All cultures of the fluid were negative. The signs of tamponade and heart failure rapidly subsided. She was treated with digitalis and diuretics and discharged after one month.

She did well for 2 months but had to be readmitted with recurrent signs and symptoms of tamponade. The blood pressure was then 98/80 mm. Hg. After the removal of 2 L. of pericardial fluid the pressure stabilized at 100/60. She improved rapidly again and was discharged, but symptoms soon returned. In July, 1955, pericardiocentesis was again necessary; 2,500 c.c. of fluid was removed.

On her admission to this hospital on Aug. 16, 1955, her blood pressure was 100/65 mm. Hg, her heart tones muffled, and there was a flat percussion note over the left base posteriorly. X-rays showed a huge cardiac shadow with an air fluid level in the pericardial sac. The blood count and urinalysis were normal. On Aug. 17, 1955, an extensive pericardiectomy was performed through a median sternotomy incision. Heart function improved remarkably. The excised pericardium was 3 mm. thick, weighed 115 Gm., and measured 15 by 18 cm. in size. Pathologic study revealed chronic, nonspecific pericarditis. Four years have passed since surgery. She has remained entirely asymptomatic and is married and leading a completely normal life.

CASE 3.—The patient was a 6½-year-old white boy who was admitted to the hospital first on Dec. 14, 1956, because of swelling of the abdomen of 4½ months' duration. Shortly after the abdominal distention had been noted, the child had been admitted to another hospital where examination revealed lymphadenopathy, hepatomegaly, splenomegaly, and ascites. Some of the abdominal fluid was removed and showed nothing remarkable on examination. An inguinal node biopsy was not diagnostic. The child had had a poor appetite for a year. He had had several nosebleeds during the 6-month period prior to admission. There had been no related fever, ankle edema, or melena. He had had mumps, measles, and, at the age of 4, pneumonia. There had been no known contact with tuberculosis and there was no history of rheumatic fever. Thirteen siblings were living and well.

Examination revealed a chronically ill boy with a rounded face, marked abdominal distention, and thin extremities. He appeared uncomfortable especially in the supine position. Blood pressure was 95/70 mm. Hg. The neck veins were distended. There was generalized lymphadenopathy. The lungs were clear, the diaphragms elevated, and their excursions limited. The heart was not enlarged. The tones were slightly distant and there was a grade 1 harsh apical systolic murmur. The second pulmonary sound was louder than the aortic. There was massive ascites. No organs or masses were palpable. There was marked venous distention over the thorax and abdomen.

Cardiac fluoroscopy revealed diminished amplitude of cardiac pulsations. The left atrium, right ventricle, and right atrium were noted to be enlarged on x-ray studies. The pulmonary outflow tract was prominent and there were mild congestive pulmonary changes.

Electrocardiograms showed an abnormal QRS pattern over the right ventricle. First and second strength Mantoux tests were negative as was the histoplasmin test. Blood counts, urinalyses, and studies of liver chemistry were within normal limits. Examination of the bone marrow revealed reactive irritational abnormalities of undetermined cause. Paracentesis was performed on December 19. Two liters of cloudy, straw-colored fluid with a specific gravity of 1.017 were removed. Cultures were negative for pathogenic organisms including tubercle bacilli. No carcinoma cells were seen. Following paracentesis the liver was palpable 4 cm. below the right costal margin and the spleen two fingers below the left. Neither organ was tender. Right heart catheterization on December 21 showed a low cardiac output and a failing right ventricle as evidenced by a diastolic plateau. Cineangiography was also suggestive of constrictive pericarditis. The atria were dilated, and the ventricles restricted in their motion. The left ventricle appeared quite small.

The patient was discharged on December 22 and readmitted January 21. He had several nosebleeds at home and his abdomen increased in size. A paracentesis was performed on January 27, 2,400 c.c. of amber-colored fluid being removed. Again this was negative for bacteria and tumor cells. The venous pressure was 38 cm. H_2O; the total blood volume 2,616 c.c.

Pericardiectomy was performed on January 28 through a bilateral fifth intercostal space transsternal incision. The pericardium was calcified and the calcification extended into the myocardium in some area. The pericardium was completely removed except for a posterior shell lying against the vertebral bodies. All cardiac chambers were freed so that there was no residual inflow or outflow tract obstruction. The excised pericardium consisted of two portions, one 6.5 by 5.5 cm. in size, the other 5 by 7.5 cm. in size. Histologically it showed hyalinized fibrous tissue with foci of calcification. There were infiltrates of lymphocytes in several areas and the picture was consistent with chronic, nonspecific pericarditis.

The patient was digitalized postoperatively. His course was uneventful. Blood volume study repeated 5 days postoperatively revealed a total volume of 2,180 c.c. The reduction in total blood volume was 20 c.c. per kilogram. He was discharged on the tenth postoperative day and was continued for a while on digitoxin.

He has been followed for 2½ years and is completely asymptomatic. He has taken no medication for over a year, is active, and is doing well in school. Venous pressure is 11 cm. H_2O; blood pressure 110/70 mm. Hg. The abdomen is flat and no viscera are palpable.

CASE 4.—The patient was a 13-year-old white boy who was admitted to the hospital first on Oct. 15, 1957, because of abdominal distention and fatigue of 4 months' duration. He had been hospitalized elsewhere 10 days previously. On a routine chest film calcification around the heart had been noted. The past history revealed that he had had measles, scarlatina, and chickenpox. When he was 1½ years old he had had an undiagnosed febrile illness which lasted 3 days. Following this illness he stopped talking and subsequently a diagnosis of nerve deafness was made. He had attended a special school for deaf children. He had good mental capacity. Three siblings were normal. There was no known exposure to tuberculosis and no history suggestive of rheumatic fever.

Examination revealed a chronically ill, poorly nourished child. The blood pressure was 98/72 mm. Hg. Hearing was grossly diminished. The tympanic membranes were normal. The neck veins were prominent, the lungs were clear, the heart was not enlarged, the heart sounds were quiet, and there were no murmurs. A paradoxical pulse was easily elicited. The abdomen was moderately protuberant and ascites was present. The liver edge was palpable 6.5 cm. beneath the right costal margin. There was a mild hepatojugular reflux. The tip of the spleen was palpable. There was no peripheral edema. Cardiac fluoroscopy revealed pericardial calcification over the left ventricular area with herniation of a large left atrium. The electrocardiogram showed an abnormal QRS over the right ventricle suggesting an incomplete right bundle branch block. There were nonspecific ST-T changes over the left ventricular area. The blood count, urinalysis, and

liver function studies were normal. The first and second strength Mantoux tests were negative, as was the histoplasmin test. Right heart catheterization performed on October 24 revealed the cardiac output to be depressed at rest and in response to exercise. The right ventricular pressure was 44/22 mm. Hg with a pressure pulse pattern suggestive of constrictive pericarditis. The mean pulmonary capillary pressure was elevated to 23 mm. Hg. Cineangiographic studies revealed delayed emptying of a greatly enlarged left atrium into a small deformed left ventricle.

The patient was to have a pericardiectomy, but on October 27 he developed fever and there was clinical and x-ray evidence of bronchopneumonia and left pleural effusion. He was treated with antibiotics and made an uneventful recovery. The pleural fluid removed was negative for acid-fast bacilli. He was discharged on November 14 and was readmitted on Jan. 6, 1958.

Venous pressure was 44 cm. H_2O. Pericardiectomy was performed on January 7 through a bilateral fifth intercostal space transsternal incision. There was calcification in the thickened adherent pericardium. The pericardium was completely excised except for a small shell lying posteriorly over the vertebral area. All cardiac chambers were freed and the thick adherent pericardium in the left atrioventricular groove was completely removed. At the completion of the procedure all chambers were free and the inflow and outflow tracts were unobstructed. The excised pericardium showed histologically dense fibrous tissue infiltrated with a few plasma cells, histiocytes, and lymphocytes most marked around the small blood vessels. There were large foci of calcification.

The patient was given digitalis postoperatively. He had an uneventful convalescence. Three days after operation his venous pressure had fallen to 25 and 6 days later to 16 cm. H_2O. He was discharged on January 17. He had had excellent diuresis after operation and had lost 15 pounds. Two months later the venous pressure was 6 cm. H_2O. His exercise tolerance has steadily improved during the year and a half since treatment and he has remained entirely asymptomatic.

REVIEW OF THE LITERATURE

In Table I are listed the pertinent data from the 66 cases of pericardiectomy and 2 of "pericardiolysis" for cardiac tamponade performed upon patients in the pediatric age group. Included are our own 4 cases and all of those we have found in the literature described in sufficient detail so that it is known that they were 16 years or younger at the time of surgical treatment. There are included 2 cases of "pericardiolysis" for constrictive pericarditis performed by Hallopeau as early as 1910 and reported by Delorme.[11] Rehn[21] appears to be the first to have performed a pericardiectomy in a child. The earliest pericardiectomies in children in this country were by Beck in 1929[3] and by Churchill in 1932.[7] The youngest patient treated by pericardiectomy for constrictive pericarditis was 2½ years of age.[1] In 3 of the cases pericardiectomy was performed because of chronic cardiac tamponade during the stage of pericardial effusion; Betts' case[4] was 3 years old, Crastnopol's[8] 10, and ours, 16.

The ratio of males to females was nearly 2 to 1. Sex was not stated in a few instances. Forty-three were males and 20 were females. Harrington's report includes the largest number of operative procedures upon children[12]: there were 7 such cases. Santy[23] and Wu[30] reported 6 each. In 25 per cent of the patients, operation was carried out within 6 months after the onset of symptoms. Half of the patients were symptomatic for more than a year before operative treatment.

TABLE I. DATA CONCERNING 68 CASES TREATED BY PERICARDIECTOMY OR PERICARDIOLYSIS IN CHILDHOOD

AUTHOR	AGE	SEX	DURATION OF SYMPTOMS	ETIOLOGY		RESULT	FOLLOW-UP
				CLINICAL IMPRESSION	PATHOLOGIC DIAGNOSIS		
Andreu	2½	M	1 wk.	Tuberculosis	Nonspecific pericarditis	Cured	8 mo.
Andrews	16	F	5 yr.	Tuberculosis	Tuberculosis	Cured after second operation	15 mo.
Andrews	13	M	1 yr.	Tuberculosis	Tuberculosis	Improved	1 yr.
Andrews	12	M	2½ yr.	Tuberculosis	Tuberculosis	Died	
Andrews	6	M	2 yr.	Tuberculosis	Tuberculosis	Improved	9 mo.
Beck	14	M	1½ yr.	—	Nonspecific pericarditis	Excellent	6 mo.
Betts	3	—	2 mo.	Tuberculosis	Tuberculosis	Cured	2 mo.
Blalock	14	M	6 mo.	Staphylococcus aureus	Chronic inflammation	Died 2 wk. later	
Chambliss	14	M	—	Tuberculosis	—	Died 2 wk. after operation	
Chambliss	15	M	—	—	—	Died at operation	
Churchill	16	M	2 yr.	Rheumatic	Nonspecific pericarditis	Moderately improved; died 8 yr. after second operation	
Churchill	12	M	3 mo.	—	Nonspecific pericarditis	Cured	22 yr.
Churchill	12	F	6½ yr.	—	Nonspecific pericarditis	Cured	21 yr.
Churchill	11	F	1 yr.	—	Nonspecific pericarditis	Cured	20 yr.
Crastnopol	10	M	—	Staphylococcus aureus	—	Cured	4 yr.
Cuvelier	15	—	—	Tuberculosis	Tuberculosis	Cured	9 yr.
Delorme	16	M	—	Rheumatic	—	Cured	
Delorme	7	M	—	Suppuration	—	Improved	
Harrington	11	M	4 mo.	—	Nonspecific pericarditis	Cured	2 yr. 10 mo.
Harrington	14	F	2 yr.	—	Nonspecific pericarditis	Cured	1 yr. 7 mo.
Harrington	16	M	2 yr.	—	Nonspecific pericarditis	Improved	5 mo.
Harrington	15	M	4 mo.	—	Nonspecific pericarditis	Improved	(Died pneumonia 7 months later)
Harrington	12	M	5 yr.	—	Nonspecific pericarditis	Died 4 days	
Harrington	16	F	2 yr.	—	Nonspecific pericarditis	Died 3 days	
Harrington	12	M	2 mo.	—	Nonspecific pericarditis	Died at operation	
Heuer	15	F	5½ yr.	—	Nonspecific pericarditis	Cured	2½ yr.
Ibrahim	15	M	6 yr.	—	Nonspecific pericarditis	Cured	3 yr.
Ibrahim	11	M	9 mo.	—	Nonspecific pericarditis	Unimproved	3 yr.
Ibrahim	8	M	3 yr.	—	Nonspecific pericarditis	Improved	3 yr.
Ibrahim	11	F	4 mo.	—	Nonspecific pericarditis	Died 1 day	
Koennecke	9	M	1 yr.	—	—	Excellent	1 yr.
Kreutzer	8	F	2 yr.	Tuberculosis	Tuberculosis	Excellent	3 yr.
Kreutzer	13	F	1 yr.	Tuberculosis	Tuberculosis	Excellent	1 yr.
Lawrence	14	M	6 wk.	—	Nonspecific pericarditis	Died after third operation	
Macedo	14	F	8 yr.	Tuberculosis	Tuberculosis	Died 2 mo. after third operation; atrial septal defect	

Macedo	14	F	7 yr.	—	—	Cured	
Macedo	14	F	2 yr.	—	—	Cured	
McKusick	16	M	9 mo	Tuberculosis	Tuberculosis	Cured	
McKusick	16	M	3 mo.	—	Nonspecific pericarditis	Cured	
Mortensen	15	—	2 yr.	—	Nonspecific pericarditis	Unimproved	Died 4 yr. later
Mortensen	14	—	3½ yr.	—	Nonspecific pericarditis	Cured	6 yr.
Mortensen	15	—	2 yr.	—	Nonspecific pericarditis	Improved	10 yr.
Rehn	6	F	—	Tuberculosis	—	Temporary improvement	
Rehn	14	M	—	Rheumatic	—	Excellent	Died 1 yr. later of recurrent rheumatic fever
Rehn	13	F	—	—	—	Excellent	Died 1½ yr. later of influenza
Robertson	11	F	3 mo.	Tuberculosis	Nonspecific pericarditis	Died 1 day	
Santy	13	M	4 mo.	Tuberculosis	Nonspecific pericarditis	Died generalized tuberculosis 8 mo.	
Santy	13	F	1 yr.	Tuberculosis	Nonspecific pericarditis	Cured	3 yr.
Santy	16	M	6 mo.	Tuberculosis	Nonspecific pericarditis	Died 2 wk.	
Santy	13	M	2 mo.	Rheumatic	Nonspecific pericarditis	Excellent	
Santy	11	M	<1 yr.	Tuberculosis	Nonspecific pericarditis	Slightly improved	
Santy	13	M	<1 yr.	Tuberculosis	Tuberculosis	Cured	1 yr.
Schmieden	5	M	9 mo.	—	—	Improved	
Sellors	11	F	1 yr.	Tuberculosis	Tuberculosis	Improved	3½ yr.
Sellors	11	M	3 yr.	Tuberculosis	Tuberculosis	Died 1 day	
Westermann	6	M	—	—	—	Cured	18 yr.
Westermann	14	F	1 yr.	—	—	Cured	18 yr.
Westermann	16	M	<1 yr.	Tuberculosis	Tuberculosis	Cured	2 yr.
Wu	6	M	1 yr.	Tuberculosis	Tuberculosis	Unimproved	Died 2 mo.
Wu	16	M	4 yr.	—	Nonspecific pericarditis	Cured	5 yr.
Wu	15	M	1½ yr.	Tuberculosis	Tuberculosis	Died at operation	
Wu	6	F	5 yr.	—	Nonspecific pericarditis	Cured	1 yr.
Wu	5	M	9 mo.	Tuberculosis	Tuberculosis	Cured	2 yr.
Wu	5	M	2 yr.	—	Nonspecific pericarditis	Improved	6 mo.
Authors	16	F	7 mo.	—	Nonspecific pericarditis	Cured	4 yr.
Authors	15	M	17 mo.	Tuberculosis	Nonspecific pericarditis	Cured after second operation	7 yr.
Authors	6½	M	6 mo.	—	Nonspecific pericarditis	Cured	2 yr.
Authors	13	M	6 mo.	—	Nonspecific pericarditis	Cured	15 mo.

From the survey of the literature it is difficult to determine precisely the etiology of the pericardial disease. In more than 50 per cent of the cases there was no specific etiological factor suggested and the pathologic picture was one of nonspecific inflammatory disease. Tuberculosis could possibly be implicated as the etiological factor on a clinical basis in 26 instances (38 per cent). In 17 of them there was pathologic proof of the diagnosis, while in 7 the picture was one of nonspecific pericarditis. In 2 cases the histologic findings were not reported. Rheumatic pericarditis was suspected in 4 cases but in none was there pathologic proof. Churchill's patient[29] who died 8 years after his second operation showed evidence of chronic rheumatic endocarditis on postmortem examination. Santy's patient[23] had had four episodes of acute rheumatic fever. There was no evidence of rheumatic disease in the resected pericardium. There were three instances of suppurative constrictive pericarditis. In Blalock's case[5] which terminated fatally, *Staphylococcus aureus* was the etiological agent. Crastnopol's[8] patient was cured and Delorme's[11] improved by pericardiectomy.

The results following the initial procedure were recorded as good, excellent, or a cure in 35 cases, or 51.5 per cent. Another 12 patients were felt to be improved. Thus 47, or 69 per cent, were benefited. In 8 instances there was slight, temporary, or no clinical improvement following surgery. Twelve patients died at operation or during the early postoperative course. Four died later. One of Santy's patients died 8 months later of generalized tuberculosis. Interestingly enough, the excised pericardium in this case had revealed no microscopic evidence of tuberculosis. Two patients who were unimproved died 2 months (Wu's case) and 4 years (Mortensen's case) after operation. One of Harrington's patients who was improved by pericardiectomy died 7 months later of pneumonia.

Two children who were improved by the first procedure were subsequently cured after a second more complete removal of the pericardium (Andrews' case[2] and one of our own). Another who was unimproved after the first operation was much better after the second. This patient died 8 years later of congestive heart failure due to rheumatic heart disease.[29] Lawrence's[17] patient was not improved by a second procedure and died following the third. Macedo[18] reported a patient upon whom three operations were performed; she died 2 months after the third and was found at postmortem to have an atrial septal defect. There were 76 operations performed upon the 68 cases.

The final result after these operative procedures was good or excellent in 37, or 54.5 per cent. An additional 11 patients were improved, though one of them died 8 years later as the result of rheumatic heart disease. Forty-eight

TABLE II. RESULTS OF PERICARDIECTOMY IN CHILDREN*

RESULT	BEFORE 1945	AFTER 1945
Excellent	17 (51.5%)	20 (60.5%)
Improved	7	4
Poor or death	9 (27%)	9 (27%)
Total	33	33

*Date of treatment not stated in 2 cases.

patients, or 71 per cent, were benefited or cured. In 6 cases there was slight, temporary, or no improvement. Death at operation or shortly thereafter occurred in 14 cases (21 per cent).

When the results of treatment prior to 1945 and since that time are compared, disappointingly enough, no substantial improvement is noted (Table II).

DISCUSSION

Constrictive pericarditis is predominantly a disease of the male. In reviewing the sex incidence from several large series, Andrews[2] noticed an 80 to 90 per cent male preponderance. Approximately twice as many cases have been reported in male children as in female children. In most there was neither clinical nor pathologic evidence of any specific etiology. The commonest specific etiology suspected on clinical grounds was tuberculosis. In the majority of instances in which tuberculosis was thought to be the etiologic basis, microscopic proof was forthcoming. In 7 cases, however, the excised pericardium revealed no evidence of tuberculosis. In one such case death subsequently occurred from generalized tuberculosis. It is the general feeling that rheumatic pericarditis rarely leads to constriction.[17] Sellors[25] has pointed out that lesions resulting from rheumatic fever tend to be thin and vascular with loosely packed, wavey collagen fibers and not the heavy hyalin collagenous type which he feels are more likely to lead to cicatrization and contracture. In four instances, children were thought to have chronic constrictive pericarditis on a rheumatic basis but in no case was there microscopic proof. Suppuration was the etiological factor in 3 of the cases reviewed. We have found no instance of constriction or chronic temponade from traumatic hemopericardium in a child.

In 3 of the children pericardiectomy was performed for cardiac tamponade resulting from massive chronic pericardial effusion. The results were excellent in all. In our patient (Case 2) the etiology was obscure. In Bett's case there was tuberculous pericarditis. Crastnopol's patient had a coagulase positive *Staphylococcus aureus* infection. Experience with chronic tamponade from massive pericardial effusion in children as well as in adults leads us to believe that early pericardiectomy is the best treatment.

The over-all results of pericardiectomy in children have been reasonably satisfactory. We were disappointed, however, to find that only slightly over half of the patients have been cured or obtained a truly excellent result, and that only 70 per cent have either been made essentially well or improved significantly. There was an operative and postoperative mortality of 18 per cent after the original operation and of 21 per cent when secondary and tertiary operative procedures are included. It is particularly disappointing to find that those treated since 1945 have not had appreciably better results than those treated prior to this time. One would certainly have anticipated that in recent years the results of operative treatment in children, as well as in adults, should be substantially better. This is based upon the fact that we now have available a variety of effective antibiotics and particularly antibiotic and chemotherapeutic agents which are effective against tuberculosis. It is also based upon the

hope that surgeons have become generally impressed with the need for performing a complete operative procedure at the first session. In several of the patients included in this review, secondary operations were necessary. Two who had been significantly improved by the first procedure were cured by the second and a third was improved. In 2 cases three operative procedures were ineffectual and death occurred after the third.

Our personal experience with pericardiectomy, both in children and in adults, would lead us to believe that we can anticipate a lower mortality in the future and better over-all results. The first of our 4 patients required a secondary operation. In the last 3 the pericardiectomy was so extensive that all cardiac chambers and all inflow and outflow tracts were completely freed. We have incurred no mortality and all 4 of our young patients are clinically cured.

SUMMARY

Four cases of pericardiectomy in children for chronic constrictive pericarditis or cardiac tamponade with chronic pericardial effusion are reported. The pertinent literature concerning pericardiectomy in the pediatric age group is reviewed. The over-all results in the literature are reasonably satisfactory, but it is felt that a distinctly lower mortality and a significantly higher cure rate should be obtained in the future. From our own experience we feel that pericardiectomy should carry a very low mortality and that it should result in a cure in almost all instances except those in which some residual cardiac dysfunction persists because of intrinsic intracardiac or valvular disease.

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Editorial

CONDUCTED BY I. S. RAVDIN, M.D., AND J. GARROTT ALLEN, M.D.

Experimental Surgery

Experimental surgery has advanced from a laboratory evaluation of operative procedures to a wider area of investigation involving many subjects hitherto considered beyond the scope of the surgeon. It is not a specialty by itself, but covers a field of research related to surgery and of interest to surgeons. Its field includes such diverse subjects as oncology, neurochemistry, endocrinology, angiology, and muscle physiology in addition to studies of general phenomena of infection, shock, metabolic response to injury, and neoplasia. On the solid foundation of the fact that research in surgery is not only desirable but necessary, one can consider its objectives as follows.

The most important task is probably the widening of the scientific approach in surgery. New facts and data related to surgical practice are uncovered continuously by research in basic sciences. It is up to the surgeons to evaluate the applicability of these findings to surgery. Not only have new fields for surgery opened recently, but also the approach to many surgical problems has undergone a change as a result of better understanding of the basic principles involved.

The clinical experience in surgery provides a unique opportunity for observations in investigation of basic phenomena in many fields such as cancer research, exposure to traumatic and infectious agents, shock, and so forth. The contribution of a surgeon to research progress in these fields can be considerable, since facts, simple and obvious to him from clinical practice, might appear to others just as obscure as some physical chemistry is to surgeons.

The final objective, but not the least important, is the training of the young generation of surgeons in research. It is unlikely that a year of investigative work prescribed by most medical schools as part of a graduate training program will lead to startling experimental findings, although notable exceptions have been made. It is the contact of the future surgeon with experimental methods which is of primary value in addition to the recognized importance of research in teaching. The preparation of the mind to face research problems of the future appears to be the logical answer to the ever-increasing scope of surgery.

While the Art of Surgery seems to have reached the summit, the Science of Surgery is confronted with a new world of electronics, sputniks, and biophysics. Whether we can keep in step with these developments depends largely on progress in surgical research.

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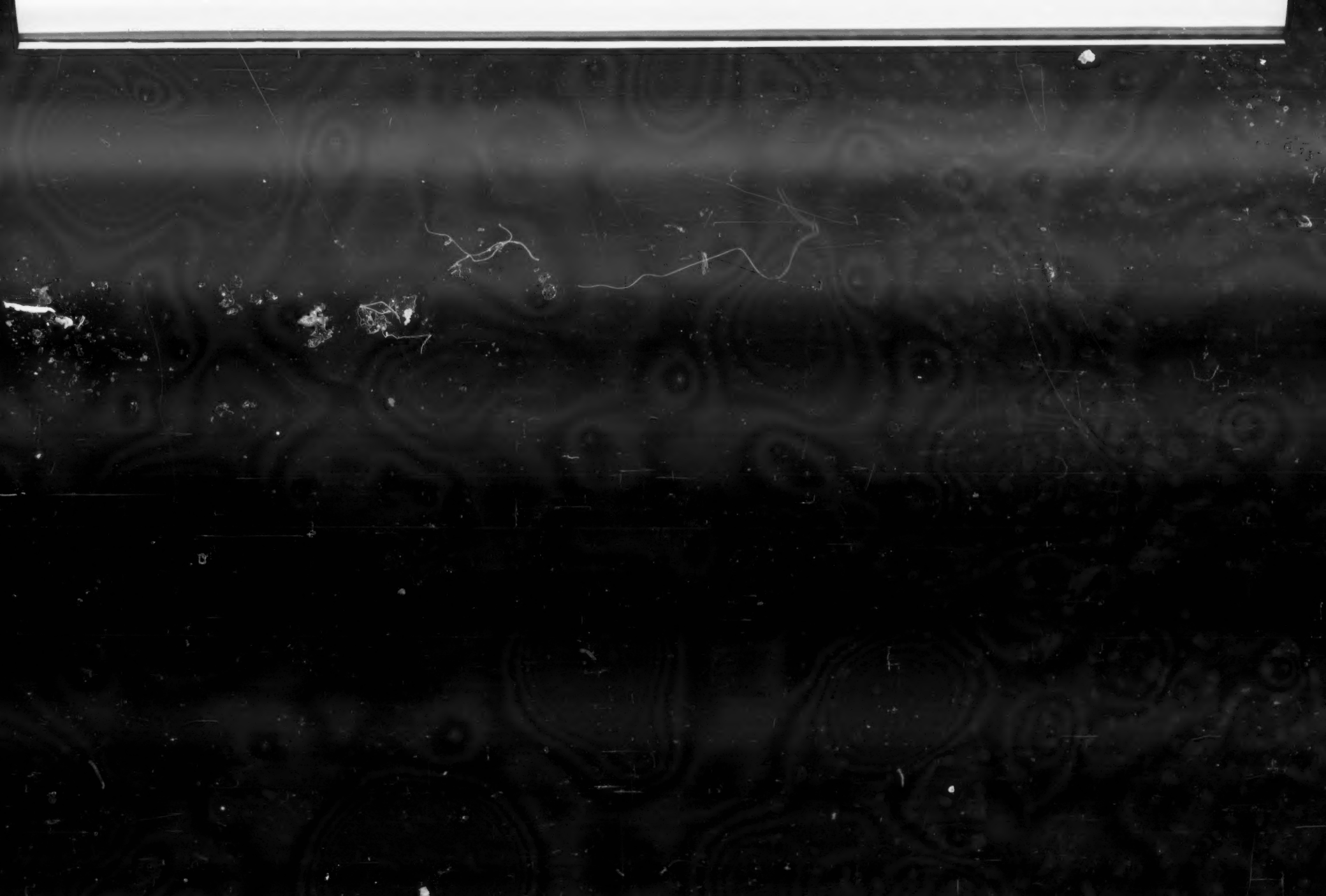

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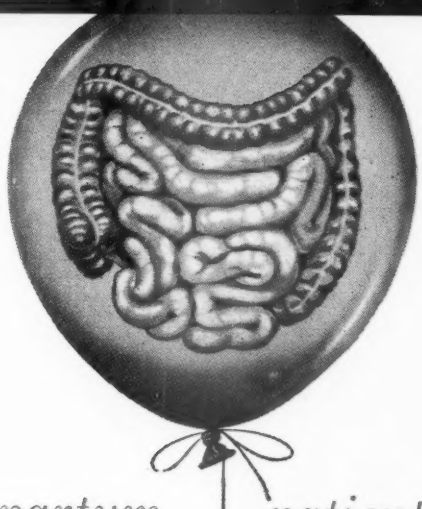

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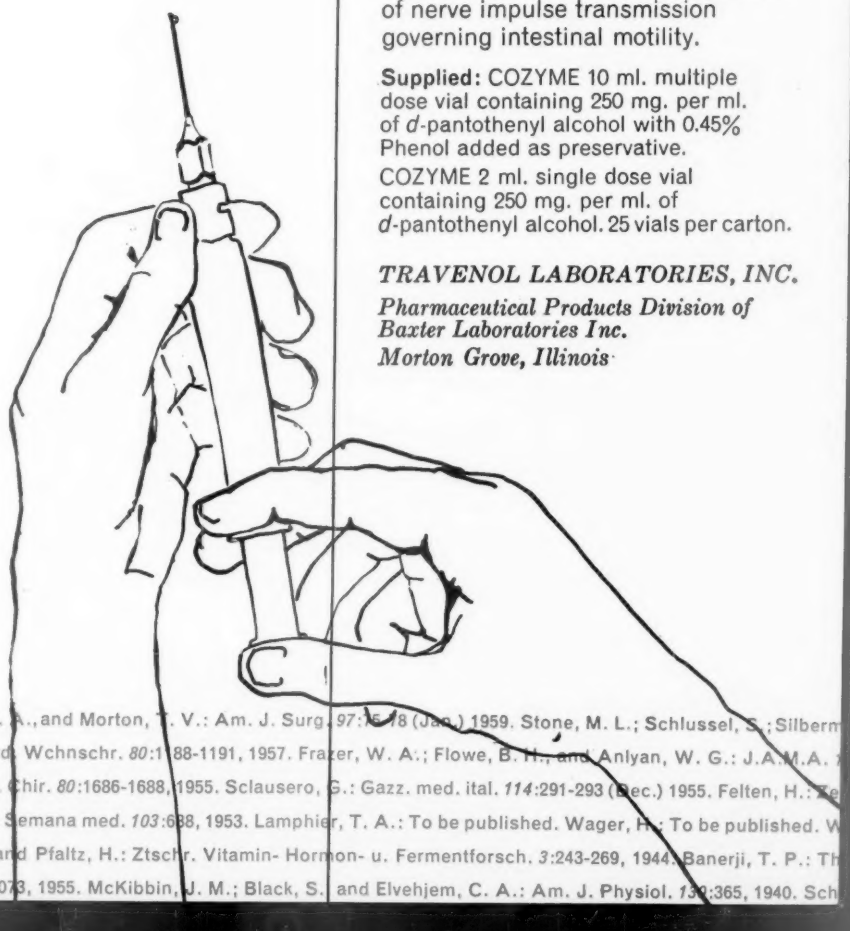

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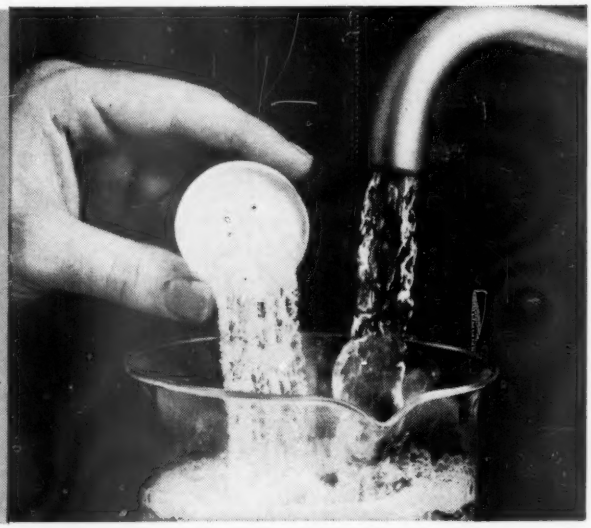

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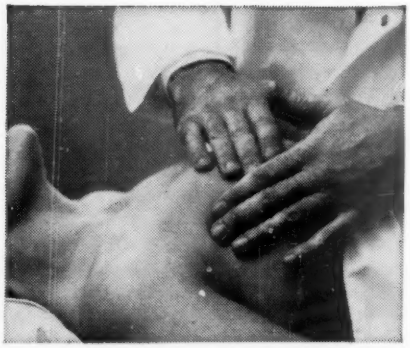

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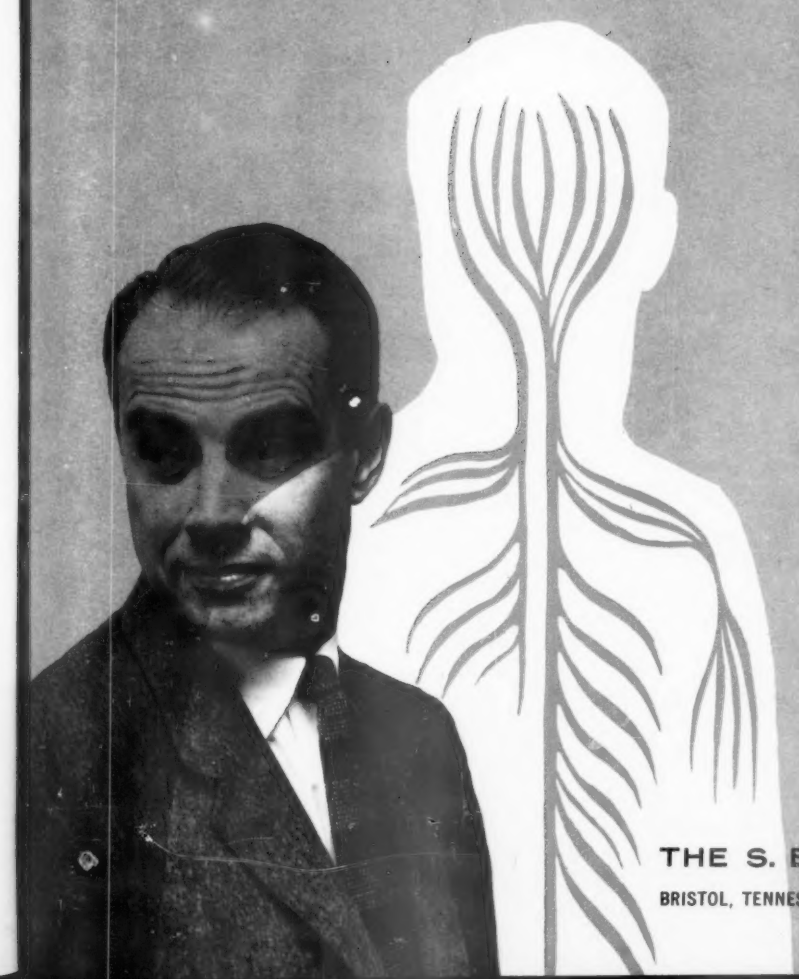

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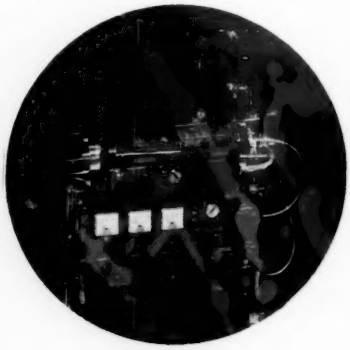

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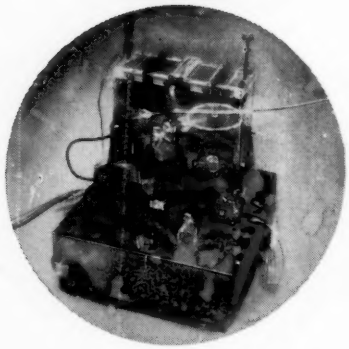

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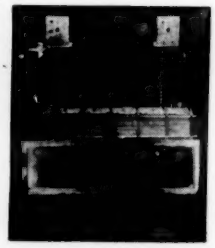

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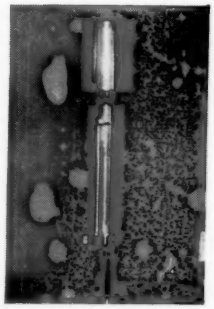

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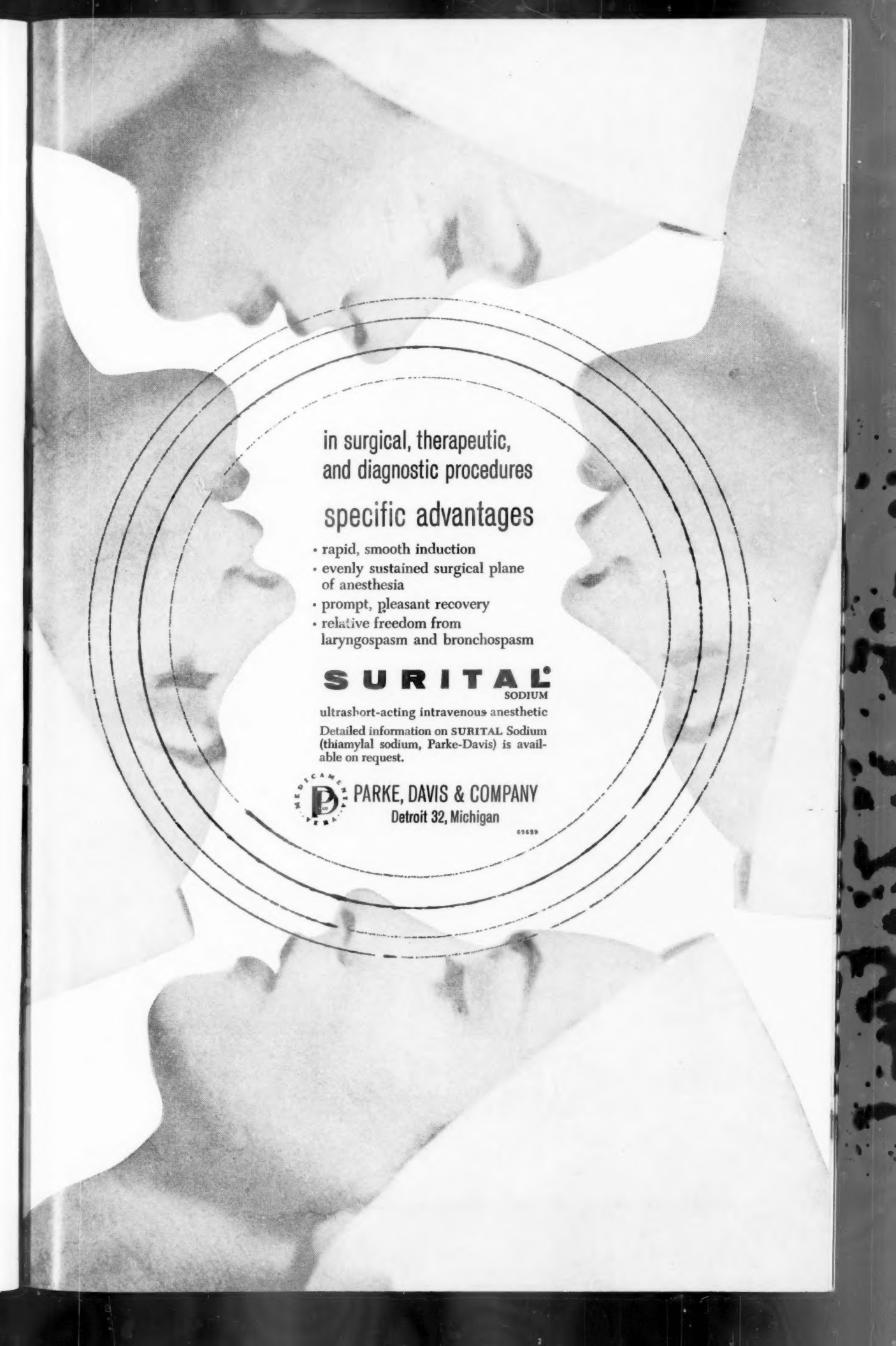
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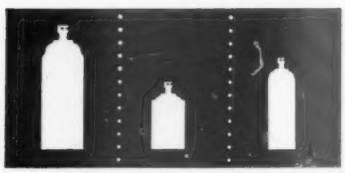

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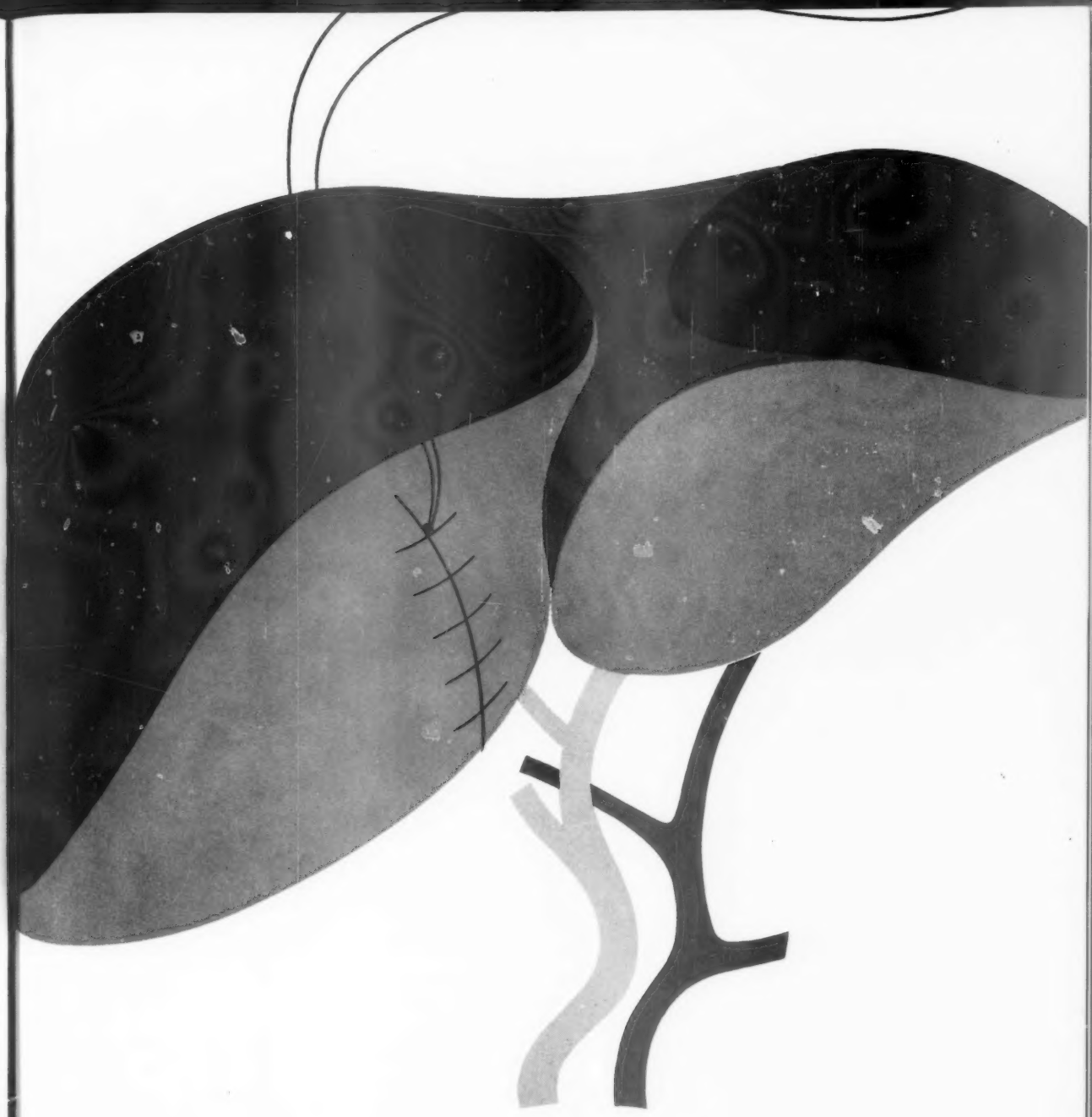

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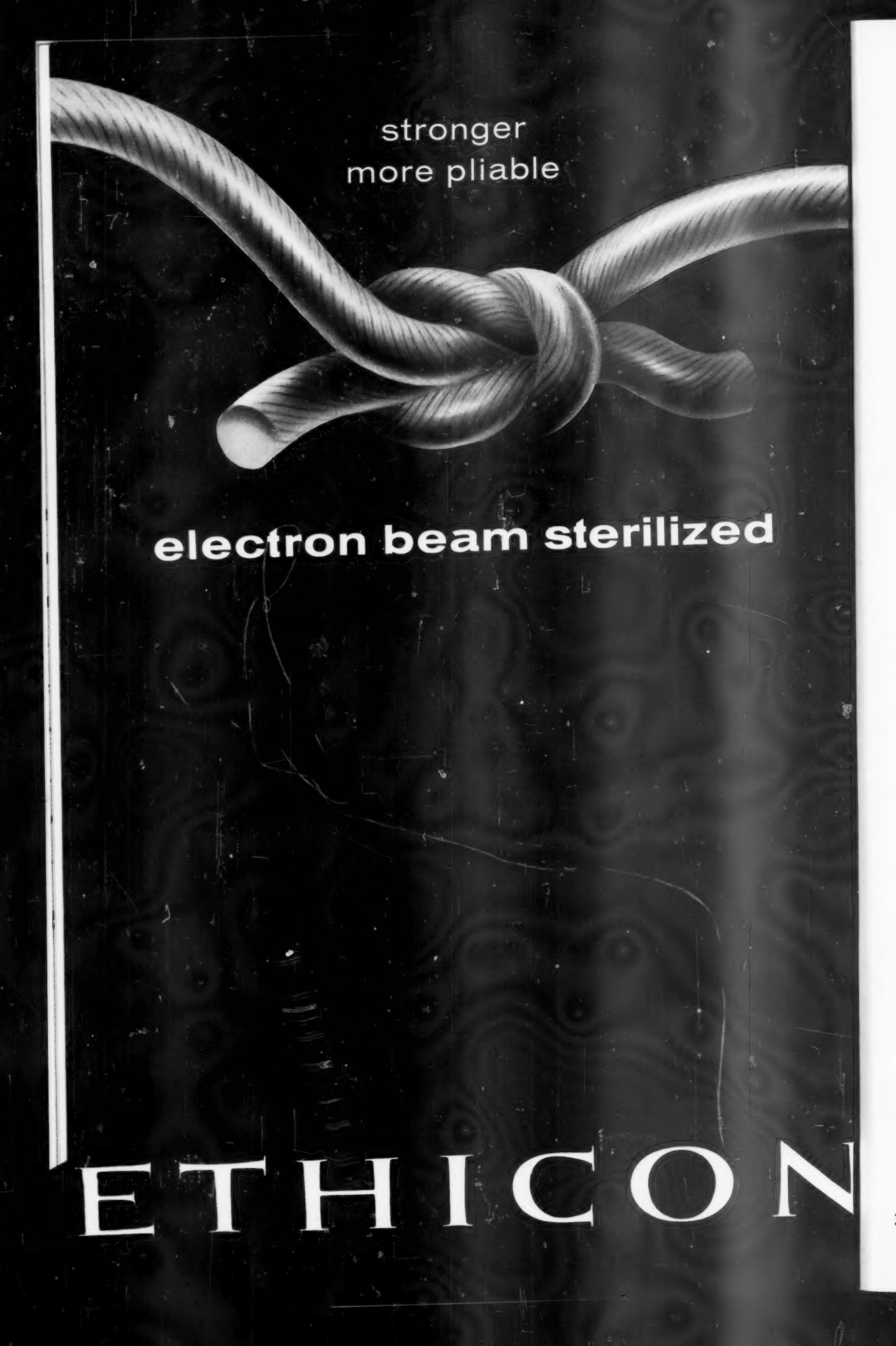
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1. Selzer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.

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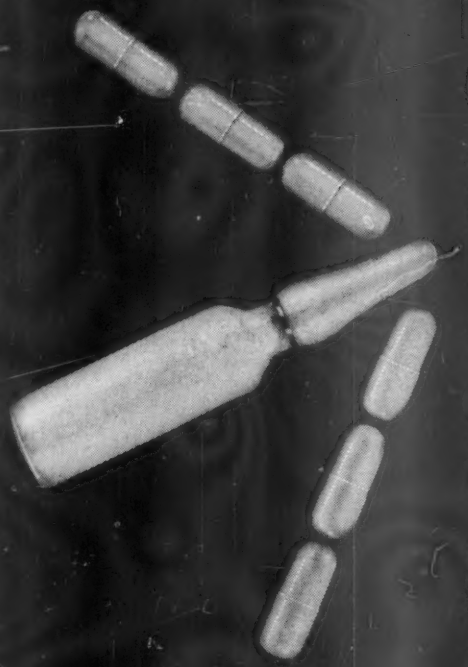

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1. Spies, T. D.: The Influence of Nutritional Processes on Aging, South. M. J., *50*:216, 1957.

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Prigot, A.; Felix, A. J., and Mullins, S.: Paper presented at the Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, September 12, 1959 (published Nov. 1959)

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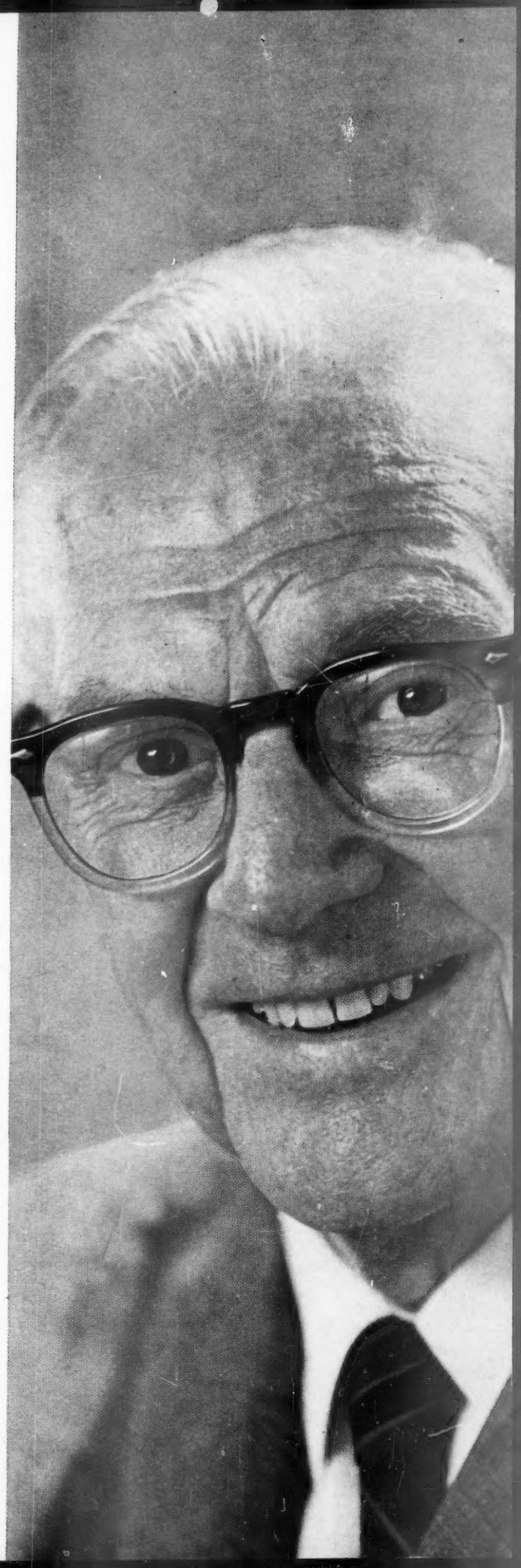

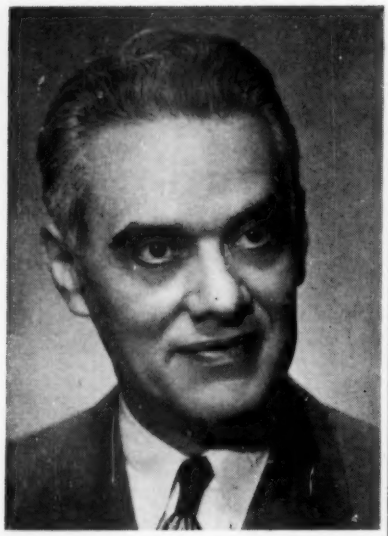

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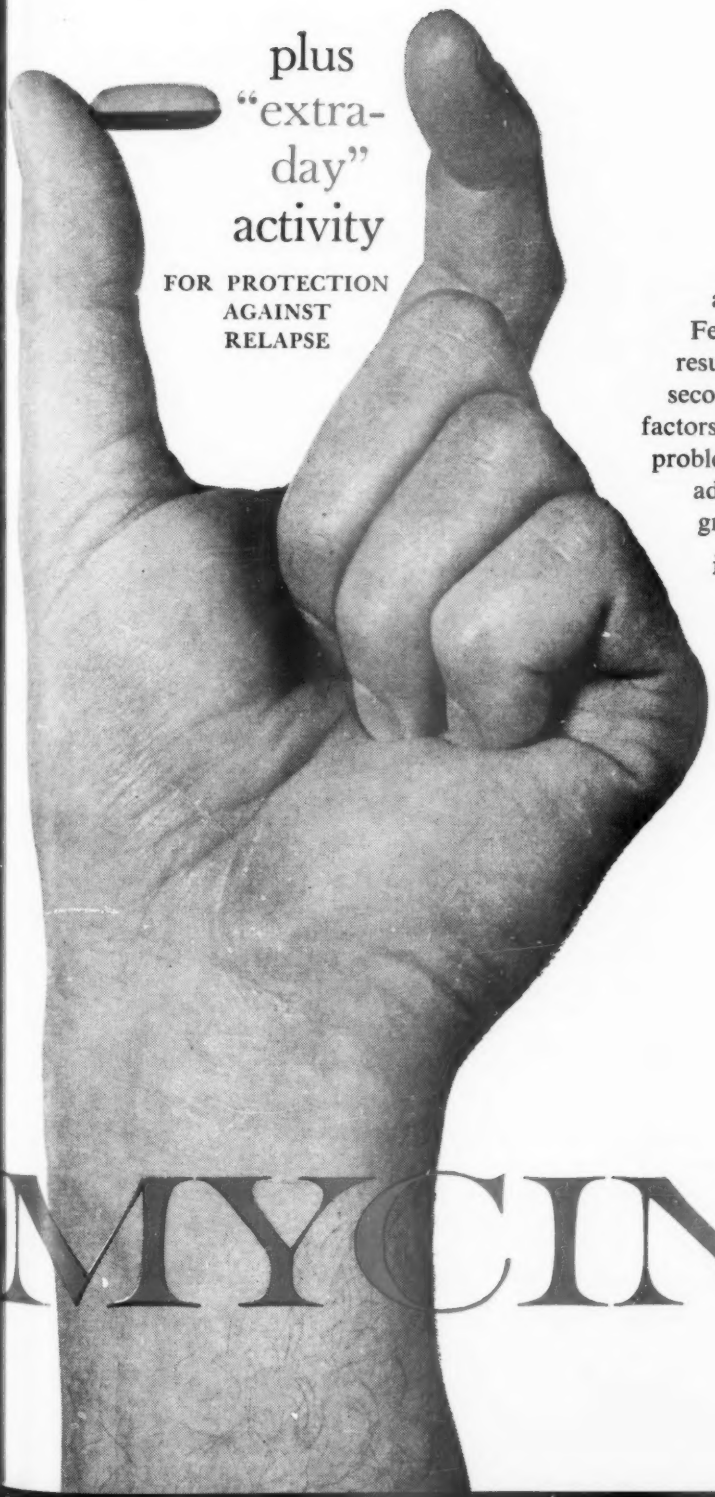

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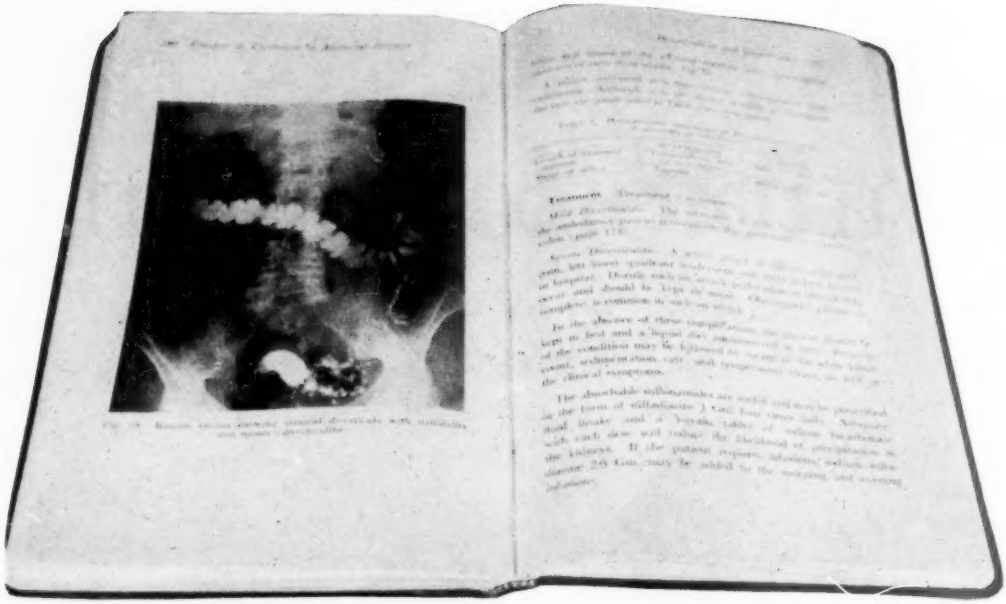

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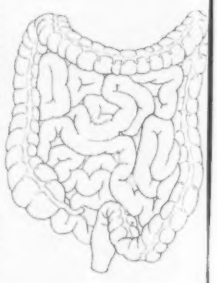

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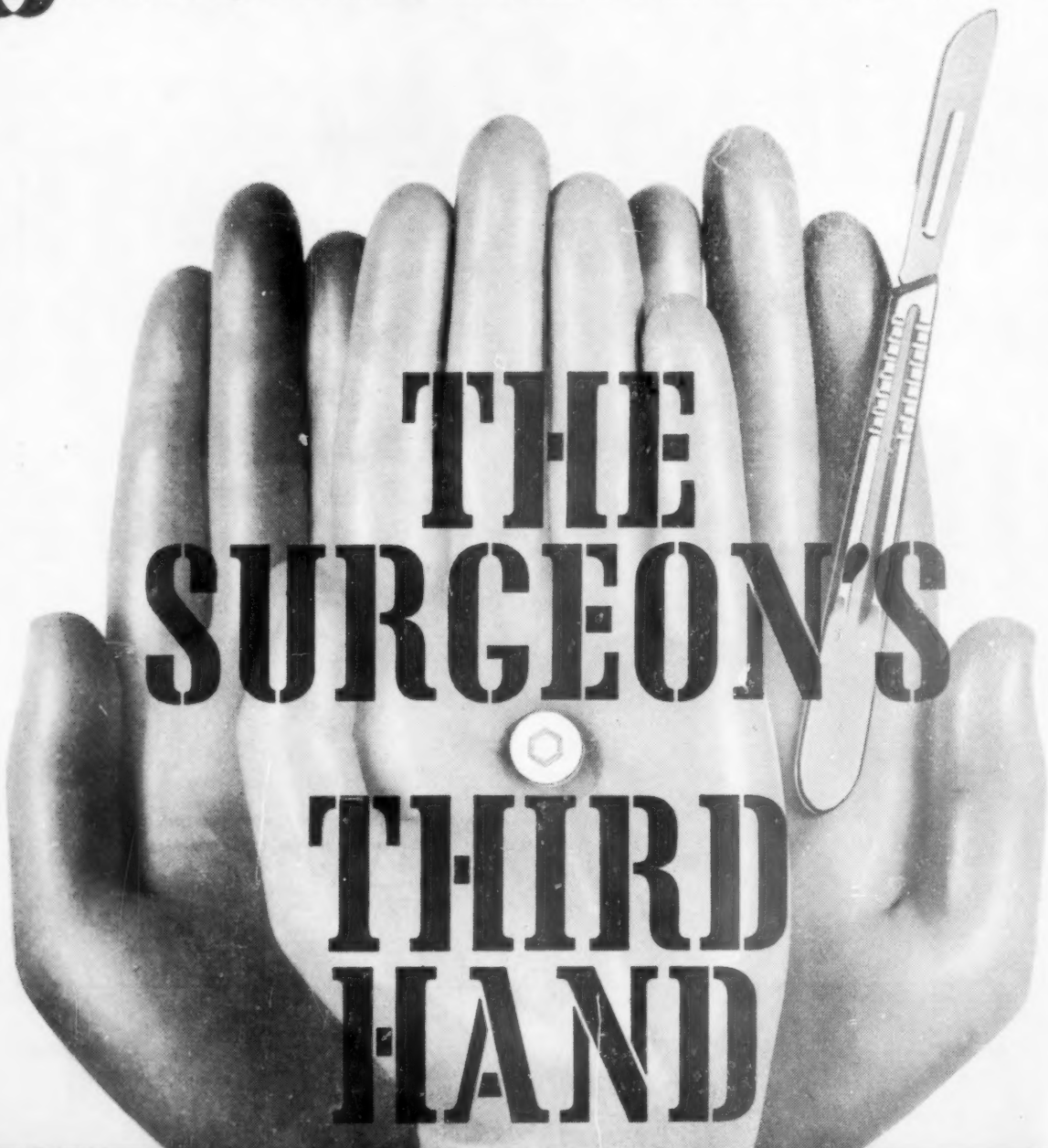

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